

PARLIAMENT OF INDIA RAJYA SABHA

59

DEPARTMENT-RELATED PARLIAMENTARY STANDING COMMITTEE ON HEALTH AND FAMILY WELFARE

FIFTY- NINTH REPORT

ON

THE FUNCTIONING OF THE CENTRAL DRUGS STANDARD CONTROL ORGANISATION (CDSCO)

(PRESENTED TO THE RAJYA SABHA ON 8th May, 2012)

(LAID ON THE TABLE OF THE LOK SABHA ON 8th May, 2012)

RAJYA SABHA SECRETARIAT

NEW DELHI

MAY, 2012 / VAISHAKHA , 1934 (SAKA)

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COMMITTEE ON HEALTH AND FAMILY WELFARE

RAJYA SABHA

- | | | | |
|-----|---------------------------|---|----------|
| 1. | Shri Brajesh Pathak | - | Chairman |
| #2. | Shri Janardhan Dwivedi | | |
| *3. | Shrimati Viplove Thakur | | |
| 4. | Dr. Vijaylaxmi Sadho | | |
| 5. | Shri Balbir Punj | | |
| 6. | Dr. Prabhakar Kore.. | | |
| 7. | Shrimati Vasanthi Stanley | | |
| @8. | Shri Rasheed Masood | | |
| 9. | Shrimati B. Jayashree | | |
| 10. | Shri Derek O'Brien | | |

LOK SABHA

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12. Shrimati Harsimrat Kaur Badal
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27. Shri J. M. Aaron Rashid
28. Dr. Arvind Kumar Sharma
29. Shri Radhe Mohan Singh
30. Shri Ratan Singh
31. Dr. Kirit Premjibhai Solanki

SECRETARIAT

Shri P.P.K. Ramacharyulu	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Deputy Director

Re-nominated to the Committee on 2nd February, 2012

* ceased to be a member w.e.f. 2nd April, 2012.

@ ceased to be a member w.e.f 9th March, 2012

SUB-COMMITTEE III ON DRAFT REPORTS - HEALTH AND FAMILY WELFARE

1. Dr. Jyoti Mirdha - CONVENOR

RAJYA SABHA

2. Shri Balbir Punj

LOK SABHA

3. Dr. Sanjay Jaiswal

SECRETARIAT

Shri P.P.K. Ramacharyulu	Joint Secretary
Shri R. B. Gupta	Director
Shrimati Arpana Mendiratta	Joint Director
Shri Dinesh Singh	Deputy Director

PREFACE

I, the Chairman of the Department-related Parliamentary Standing Committee on Health and Family Welfare, having been authorized by the Committee hereby present this Fifty-Ninth Report of the Committee on the functioning of the Central Drugs Standard Control Organisation.

2. During the course of examination of the subject mentioned above, the Committee heard the views of Secretary, Department of Health and Family Welfare along with the representatives of the Central Drugs Standard Control Organisation (CDSCO) on the 5th January, 25th July and 12th October, 2011.

3. During the course of the finalization of its Report, the Committee relied upon the following documents / papers received from the Department of Health and Family Welfare:-

- (i) Status Note;
- (ii) Questionnaire Part I and II on the functioning of CDSCO; and
- (iii) Questionnaire Set I and II on the functioning of CDSCO.

4. The Committee at its meeting held on the 4th May, 2012 considered and adopted the Draft Report.

5. The Sub-Committee III on Draft Reports considered and adopted the Report at its meeting held on 11th April, 2012.

6. For facility of reference and convenience, observations and recommendations of the Committee have been printed in bold letters in the body of the Report.

NEW DELHI

4th May, 2012

Vaishakha 14, 1934 (Saka)

BRAJESH PATHAK

Chairman,

Department-related Parliamentary

Standing Committee on Health and
Family Welfare

REPORT

INTRODUCTION

1. Drug Regulation

1.1 Drugs are an integral and inseparable part of medical care. As per the directory of pharmaceutical manufacturing units in India brought out by the National Pharmaceutical Pricing Authority in 2007, more than 10,500 drug manufacturers are operating in the country with estimated turnover of just over Rs. 50,000 crore for domestic sale alone.

1.2 Medicines apart from their critical role in alleviating human suffering and saving lives have very sensitive and typical dimensions for a variety of reasons. They are the only commodity for which the consumers have neither a role to play nor are they able to make any informed choices except to buy and consume whatever is prescribed or dispensed to them because of the following reasons:

- Drug regulators decide which medicines can be marketed;
- Pharmaceutical companies either produce or import drugs that they can profitably sell;
- Doctors decide which drugs and brands to prescribe;
- Consumers are totally dependent on and at the mercy of external entities to protect their interests.

1.3 It is because of these typical dimensions that the state's responsibility to regulate the import, manufacture and sale of medicines so as to ensure that they are both safe, effective and of standard quality acquire almost sacrosanct dimensions. Under the circumstances, effective, transparent drug regulation free from commercial influences is essential to ensure the safety, efficacy and quality of drugs with just one objective, *i.e.*, welfare of patients.

1.4 Taking into account the immense importance and impact of drug regulation on humanity, the Committee examined the functioning of The Central Drugs Standards Control Organisation (CDSCO), the agency mandated with the task of drug regulation in India to determine if rules and laws were being implemented efficiently and honestly in the interest of patients. It did not go into the scientific issues such as merits of medicines being sold in the country. As the successive

narrative would unravel, the drug regulatory system in the country suffers from several deficiencies and shortcomings, some systemic and several manmade.

1.5 Drug regulation covers many functions, namely:

- Marketing approval of new medicines based on safety and efficacy studies,
- Licensing and monitoring of manufacturing facilities and distribution channels,
- Post-marketing adverse drug reaction (ADR) monitoring,
- Quality control (QC),
- Periodic review and re-evaluation of approved drugs,
- Control of drug promotion
- Regulation of drug trials.

1.6 While most functions pertaining to drug regulation come under the jurisdiction of Central Government and are carried out by the Central Drug Standards Control Organization (CDSCO), others viz. licensing and monitoring of manufacturing units and distribution channels; quality control etc. are carried on by state level drugs authorities under the administrative control of state governments.

1.7 Drugs and Cosmetics Act 1940 and Rules 1945, Drugs & Magic Remedies (Objectionable Advertisements) Act 1954 as amended from time to time are the principal legislations that govern the functioning of CDSCO and state drug authorities.

1.8 Drugs belonging to various systems of medicine (Allopathy, Homoeopathy, Ayurveda, Siddha and Unani) as well as cosmetics are regulated by CDSCO. However the present Report is confined to the aspect of regulation by the CDSCO and related agencies of drugs used in modern medicine only.

2. Mandate and Structure of CDSCO

2.1 In its Status Report on CDSCO, the Ministry of Health and Family Welfare stated that the mission of CDSCO was to “meet the aspirations.... demands and requirements of the pharmaceutical industry.” As against this, the stated missions of Drug Regulatory Authorities of developed countries are as follows:

United States: The Food and Drugs Administration (USFDA) mission is, “protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs.”

United Kingdom: The Medicine and Healthcare Regulatory Authority's (MHRA) mission is "to enhance and safeguard the health of the public by ensuring that medicines and medical devices work, and are acceptably safe."

Australia: The mission statement of Therapeutic Goods Administration (TGA) states: "Safeguarding public health & safety in Australia by regulating medicines...."

2.2 The Committee is of the firm opinion that most of the ills besetting the system of drugs regulation in India are mainly due to the skewed priorities and perceptions of CDSCO. For decades together it has been according primacy to the propagation and facilitation of the drugs industry, due to which, unfortunately, the interest of the biggest stakeholder i.e. the consumer has never been ensured. Taking strong exception to this continued neglect of the poor and hapless patient, the Committee recommends that the Mission Statement of CDSCO be formulated forthwith to convey in very unambiguous terms that the organization is solely meant for public health.

2.3 The Ministry, in the status note, has stated that CDSCO, headed by the Drugs Controller General (India) [DCGI] in the Directorate General of Health Services under the Ministry of Health and Family Welfare is responsible for performing regulatory functions under the Drugs and Cosmetics Act, 1940 and Rules.

2.4 The Committee has noted that the CDSCO with its Headquarters at New Delhi has six zonal offices situated at Mumbai, Chennai, Kolkata, Ghaziabad, Hyderabad, Ahmedabad and three sub-zonal offices at Bangalore, Jammu and Chandigarh for performing certain activities in coordination with the State Drug Authorities. It has offices at 11 seaports/airports at Mumbai (sea and airport), Nhava Sheva (sea port), Kolkata (sea and airport), Chennai (sea and airport), Hyderabad (Airport), Delhi (Airport), Kochi (seaport) and Ahmedabad (airport), to regulate the import and export of drugs and cosmetics. It has six drug-testing laboratories situated at Kolkata, Mumbai, Chennai, Guwahati, Chandigarh and Hyderabad.

2.5 The Ministry has further informed the Committee that CDSCO performs the following functions at its Headquarters:

- i Grant of approval to manufacture and/or import of new drugs including vaccines and bio-therapeutic products after examining their safety and efficacy.
- ii. Grant of permission to conduct clinical trials.
- iii. Approval of the licenses to manufacture certain categories of drugs as Central License Approving Authority (CLAA), i.e., blood banks, large volume parenterals, vaccines/sera, r-DNA derived products, in-vitro diagnostic kits for detection of HIV1 & 2, HCV & HBsAg and notified medical devices.
- iv. Registration of foreign manufacturers whose products are to be imported into the country, in respect of drug formulations / Bulk drugs, Medical Devices, Blood products.
- v. Grant of licenses to import drugs in the country.
- vi. Grant of Test Licenses for import of drugs for the purpose of examination, test and analysis.
- vii. Grant of licenses to import drugs by Government hospitals or Medical Institutes for the use of their patients.
- viii. Grant of permissions for manufacture of drugs for the purpose of exports which are otherwise not permitted to be manufactured in the country.
- ix. Convening the meetings of Drugs Technical Advisory Board (DTAB) to discuss matters arising out of the administration of the D&C Act and the Rules and recommend amendments, if required.
- x. Convening the meetings of the Drugs Consultative Committee (DCC) to secure uniformity throughout India in the administration of this Act and Rules.
- xi. Coordinating the activities of the State Drug Authorities and advising them on matters relating to uniform administration of the Act and Rules in the country.
- xii. Monitoring of adverse drug reactions as a part of Pharmacovigilance programme.
- xiii. Recommend banning of drugs considered harmful or sub-therapeutic under Section 26A of the Drugs and Cosmetics Act.
- xiv. Clinical trial site inspections.
- xv. Conducting workshops and training programs in respect of various issues related to quality control of drugs.

2.6 The Committee noted from the background note that the zonal/sub-zonal offices perform the following functions:

- Inspection of manufacturing premises jointly with State Drug Authorities for drugs covered under the CLAA Scheme, i.e., IV Fluids, large volume parenterals, vaccine & sera, blood & blood products, r-DNA products (biotech products), etc., for the purpose of grant/renewal of licenses.
- Inspection of private testing laboratories in coordination with the State Drug Inspectors for approval of these laboratories for carrying out tests on drugs/cosmetics on behalf of the licensees.

- Inspection of manufacturing facilities of the firms for grant of WHO GMP Certification Scheme.
- Inspection of firms for capacity assessment and other provisions at the request of the Central Government.
- Inspections to investigate complaints received from various forums.
- Coordination with the State Drug Authorities to sort out problems involved in the investigations of drugs manufactured in one State and declared “Not of Standard Quality” in another State and other such matters.
- Launching of prosecutions in cases detected by the zonal offices of CDSCO.

2.7 According to the Ministry, the Airport and Seaport Offices monitor and regulate import and export of drugs and cosmetics and also draw samples for verifying the quality.

2.8 The Central Drug Testing Laboratories perform the following functions:

- i To undertake the testing / analysis of drugs and cosmetics;
- ii Act as an Appellate Authority for the class of drugs notified under the Act; and
- iii. Central Drug Laboratory, Kolkata maintains reference standards as per Indian Pharmacopoeia for testing of drugs.

2.9 The Ministry also stated that the activities of zonal/sub-zonal and port offices have been harmonized in a manner so as to strengthen CDSCO during the last two years. Comprehensive guidelines for harmonization of activities of zonal/sub zonal/port offices of CDSCO have been prepared and came into effect on 1.6.2011. These are available on CDSCO website.

2.10 The Committee was also informed that the following functions have been delegated to the zonal offices of CDSCO w.e.f. 1.6.2011.

- i. Grant of NOC for obtaining licence from State Drug Authority to manufacture drugs for examination, test and analysis purpose.
- ii. Grant of NOC for manufacture of unapproved/approved new drugs and banned drugs for the purpose of exports.
- iii. To grant permission for import of small quantities of drugs for personal use as per Drugs and Cosmetics Rules.
- iv. NOC for import of dual use items not for medicinal use.

2.11 On a query as to how far CDSCO has been successful in carrying out its wide-ranging regulatory functions, the Ministry stated that CDSCO with limited manpower and infrastructure is carrying out functions assigned to it to the best of its capabilities. The Ministry, however, felt that to meet the aspirations of industry and other stakeholders and bringing it at the level of developed countries, a strong, well-equipped, independent and professionally managed CDSCO is the need of the day. The pharmaceutical industry is growing at the rate of approximately 10% per year. The Ministry stated that the workload of CDSCO is increasing at the rate of approximately 20% per year while there is no corresponding rise in the manpower and infrastructure to meet the demand of the industry and discharge mandatory functions.

2.12 The Ministry, explaining about the initiatives taken to strengthen the CDSCO stated that it is being expanded to meet the requirements of the pharmaceutical industry. Two sub-zonal offices at Hyderabad and Ahmedabad have been converted into zonal offices. Three new sub-zonal offices at Bangalore, Jammu and Chandigarh have been set up to cater to the need of the pharmaceutical industry.

2.13 It was also stated that in order to maintain quality of drugs stored at the Air Ports for import or export, pharmaceutical zones at Delhi, Hyderabad and Mumbai Air Ports are being set up for proper storage of drugs.

2.14 On being asked to comment as to whether CDSCO (Hqrs) has the requisite infrastructure, the Committee was informed that there were four Deputy Drugs Controllers and five Assistant Drugs Controllers in Headquarters. These nine officers have to handle each year the work load of approximately 20,000 applications, over 200 meetings, attending to 11,000 public/industry representatives, responding to 700 parliament questions, around 150 court cases etc. Further, these nine officers also attend the meetings of DTAB and its sub-committees, Drugs Consultative Committee, National List of Essential Medicines (NELM), prepare the guidance documents on various subjects, provide inputs for amendments of Drugs and Cosmetics Act and Rules, build up pharmacovigilance programme, train the newly recruited staff and attend any other tasks assigned by Director-General of Health Services or Ministry of Health and Family Welfare, from time to time. Each officer, thus, handles multiple responsibilities and is in charge of various sections of

different technical requirements leading to their being overburdened and overstretched.

2.15 The Ministry is of the opinion that there is very poor infrastructure to handle matters like budget, recruitment, administration, and procurement. On a question as to whether there exists any effective mechanism by which the CDSCO Headquarters is in a position to co-ordinate and monitor the functioning of its zonal offices, sub-zonal offices, sea ports & airports offices and drug testing laboratories, the Ministry stated that CDSCO, at present, does not have a separate division for coordinating activities of all these offices. It is, however, proposed to have a separate division to coordinate such activities as and when the manpower is available. It was also brought to the notice of the Committee that there is a need for computer management system and video conferencing facilities for quick availability of information, creation of database and better co-ordination between the offices by linking through the networking managed by a professional agency.

2.16 Explaining about the steps taken to strengthen the manpower at CDSCO, the status of various posts sanctioned/created/proposed has been given as under:

No. of permanent posts as on 2008	No. of new posts created in 2008 and 2009	No. of additional proposed posts
111	216	1045

2.17 The Committee noted that the permanent staff, in position, as on October, 2011 is 124 out of 327 sanctioned posts. Besides, 140 contractual staff are working at the Headquarters of the CDSCO. It was also stated that filling up of 203 vacant posts in CDSCO through UPSC, in consultation with the Ministry, was being done and filling up of following posts was in process including:

- 2 posts of Joint Drugs Controller (India) [JDC(I)] being filled up by deputation through UPSC.
- 5 posts of Deputy Drugs Controller (India) [DDC(I)] being filled up by direct recruitment through UPSC.
- 16 posts of Assistant Drugs Controller (India) [ADC(I)] being filled up by deputation through UPSC.
- 100 posts of Drug Inspectors being filled up by direct recruitment through UPSC.
- 31 posts of Assistant Drugs Inspectors being filled up by direct recruitment through Staff Selection Commission.

2.18 In regard to appointment of medical doctors in CDSCO, the Health Secretary

informed the Committee that the doctors do not wish to join CDSCO. It was further stated that though recruitment rules provide for appointing people with MBBS Degree or/with pharmacology, microbiology, but usually, there was no response from the persons from these fields.

2.19 The Committee notes with serious concern that CDSCO is substantially under-staffed. Of the 327 sanctioned posts, only 124 are occupied. At this rate, what would be the fate of 1,045 additional posts that have been proposed is a moot point. If the manpower requirement of the CDSCO does not correspond with their volume of work, naturally, such shortage of staff strains the ability of the CDSCO to discharge its assigned functions efficiently. This shortcoming needs to be addressed quickly. Consideration can also be given to employ medically qualified persons as Consultants/Advisers (on the pattern of Planning Commission) at suitable rank.

2.20 The Committee also gathers that the average time taken for the completion of recruitment process is approximately 12 to 15 months. The Committee, therefore, recommends that to overcome the staff shortage, the Ministry should engage professionally qualified persons on short-term contract or on deputation basis until the vacancies are filled up. Due to the very sensitive nature of regulatory work, great care will need to be taken to ensure that persons employed for short periods did not and will not have Conflict of Interest for a specified period.

2.21 At the same time, the optimal utilization of the current staff in the best interest of public is the responsibility of those who run the CDSCO. In a resource-constrained country like India, it is extremely difficult to meet the demands, however, genuine, of all the State entities in full. Hence, prioritization is the key. For example, work relating to an application for Marketing Approval of a New Drug that will be used by millions and thus have an impact on the well being of public at large in India for years to come, is far more important and urgent than giving permission to a foreign company to conduct clinical trials on an untested new patented, monopoly drug.

2.22 The Committee also observes that the strengthening of drugs regulatory mechanisms cannot be achieved by manpower augmentation alone. A host of

issues involving capacity-building of CDSCO like upgradation of existing offices, setting up of new offices, creation of new central drugs testing laboratories and equipping them with the state-of-the-art technology to enable them to carry out sophisticated analysis of drugs, upgradation of the existing 6 Central Drugs Testing Laboratories, skill development of the regulatory officials, implementation of an effective result-oriented pharmacovigilance programme drawing on global experience, increased transparency in decision-making of CDSCO etc. will have to be addressed before the desired objectives are realized.

2.23 In the absence of any reasons for unwillingness on the part of medically qualified persons to join CDSCO, the Committee is of the opinion that emoluments and perquisites may not be the main or only reason. It is noticed that minimum prescribed academic qualifications for the post of DCGI is barely B.Pharm. On the other hand for Deputy Drugs Controller (DDC), the prescribed minimum qualification is post-graduation for medically qualified persons. The stumbling block is the requirement that DCGI should have experience in the “manufacture or testing of drugs or enforcement of the provisions of the Drugs and Cosmetic Act for a minimum period of five years.” This requirement virtually excludes even highly qualified medical doctors from occupying the post of DCGI. Moreover the rule stipulates that doctors with post-graduation should be either in pharmacology or microbiology only, thus excluding post-graduates, even doctorates (like DM) in a clinical subject. Besides, highly qualified medical doctors may be reluctant to work under and report to a higher officer with lesser qualifications in a technology driven regulatory authority set-up. Unless these concerns are addressed, it would be difficult to get the desperately required medically qualified professionals on the rolls of CDSCO.

3. Qualification and Powers of DCGI

3.1 The drug sector has two distinct manifestations nowadays. On one hand, drugs development and manufacturing is a very capital intensive and long term affair, on the other, the end product is to be made available to a multitude of very differently placed people so as to ensure their health and well being. In such a peculiar situation, the role of the drugs regulator has undoubtedly assumed critical significance. S / he has to be an outstanding professional of proven merit and standing who ensures that the massive investment compulsions of the drugs

industry never outweigh the public health interests. With this aim in mind, the Committee went into details of qualifications and experience of Heads of National Drugs Regulatory Authorities of United States and United Kingdom.

3.2 The Commissioner of United States Food and Drugs Administration (USFDA) is an experienced medical doctor, scientist, and public health specialist. After doing medical course at Harvard Medical School, she conducted research on neuroscience at Rockefeller University, studied neuron pharmacology at the National Institute of Mental Health, and later focused on AIDS research as an Assistant Director of the National Institute of Allergy and Infectious Diseases. In 1994, she became one of the youngest persons ever elected to the Institute of Medicine. In 1997, at the request of the then President of USA, she accepted the position of Assistant Secretary for Policy and Evaluation in the U.S. Department of Health and Human Services (HHS) before taking over as chief of USFDA.

3.3 The Committee also noted that the current Chief Executive of the British Medicine and Healthcare Regulatory Authority (MHRA) is a professor qualified in medicine from Cambridge, followed by post-graduation and epidemiological training at Harvard School of Public Health in the United States. He then taught as Senior Lecturer in Clinical Pharmacology at Leicester University. His clinical and research interests have been in coronary heart disease. He was the Regional Director of Research and Development, National Health Service Executive, Trent. Before taking up the current position in MHRA, he was the Director, NHS Health Technology Assessment Program.

3.4 Compared to the above, the academic qualifications of the Licensing Authority (i.e. Drugs Controller General, India) are specified in Rule 49A and 50A of the Drugs and Cosmetic Rules. As per these Rules, the Licensing Authority (DCGI) should be (a) a graduate in pharmacy or pharmaceutical chemistry (B.Pharm) or (b) a graduate in medicine with specialization (post-graduation) in clinical pharmacology or microbiology (MD) with five years' experience.

3.5 The Ministry informed the Committee that the Mashelkar Committee, 2003, had recommended for providing financial power to the DCGI at par with heads of CSIR and ICMR. The specific observation of the Mashelkar Committee is that the functions of CDSCO involve considerable sourcing of expertise from external experts

and institutions. It is necessary that such consultations are managed speedily, since drug regulatory activities are very time-sensitive. This would require provision of sufficient funds at the disposal of DCGI to make payments of honorarium and travel expenses without delay, as per the systems available with CSIR and ICMR.

3.6 The Committee fails to understand as to how a graduate in pharmacy or pharmaceutical chemistry (B.Pharm) is being equated with a medical graduate with MD in Pharmacology or Microbiology. Apart from the obvious anomaly, with rapid progress in pharmaceutical and biopharmaceutical fields, there is urgent need to revise the qualifications and experience as minimum eligibility criteria for appointment as DCGI. The Committee is of the view that it is not very rational to give powers to a graduate in pharmacy, who does not have any clinical or research experience to decide the kinds of drugs that can be prescribed by super specialists in clinical medicine such as those holding DM and PhD qualifications and vast experience in the practice of medicine and even research.

3.7 On a larger plane, the Committee is disillusioned with the qualifications provided in the age old Rules for the head of a crucial authority like CDSCO. The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK. There is, therefore, an urgent need to review the qualifications, procedure of selection and appointment, tenure, emoluments, allowances and powers, both administrative and financial of the DCGI. While doing so, the Government may not only rely on the Mashelkar Committee Report which recommended augmented financial powers to DCGI but also take cue from similar mechanisms functioning in some of the developed countries like USA, UK, Canada, etc in order to ensure that only the best professional occupies this onerous responsibility. The Committee should be kept informed of the steps taken to address this issue.

3.8 In the considered opinion of the Committee, there can never be a more opportune time than now, to usher in these changes recommended by it. The post of DCGI is vacant as of now, with an official holding temporary charge. They, therefore, desire that the government should take immediate measures in terms of their instant recommendations to ensure that CDSCO is headed by an eminent and professionally qualified person.

4. Role of the State Drug Regulatory Authorities

4.1 In reply to a query, the Ministry has informed the Committee that the condition of state drugs regulatory systems is a matter of serious concern. The Committee was informed that in order to make the State Governments appreciate their responsibilities and obligations and for strengthening their licensing and enforcement apparatus, the issue was discussed in the 39th meeting of the Drugs Consultative Committee held on 10 December, 2008 and in the Conference of the State Health Ministers and Health Secretaries held at Hyderabad from 11 to 13 January, 2011. One of the key resolutions adopted in the aforesaid Conference was that the Centre and State Governments should draw up a time-bound action plan for creation of new posts and filling up of vacant posts mainly of Drugs Inspectors and upgradation of Drugs Testing Laboratories.

4.2 The Ministry also informed the Committee that the Mashelkar Committee in 2003 had recommended one drugs inspector per 50 manufacturing units and one drugs inspector per 200 sales/distribution outlets for effective implementation of functions assigned to them. It was also informed that there were approximately 600,000 retail sales outlets and around 10,500 manufacturing units in the country, which, require just over 3,200 Drugs Inspectors. However, in reality, there were only 846 Drugs Inspectors in place against 1,349 sanctioned posts in States. Hence, the main problem faced by the States Drug Authorities was inadequate infrastructure, shortage of drugs inspectors, non-existence of data bank and accurate information, non-uniformity of enforcement among the states and lack of pro-active interaction between the States particularly, in connection with investigations relating to drugs found 'Not of Standard Quality'.

4.3 The Committee, during the visit to Bangalore, had interaction with the representatives of the State Drugs Control Department. The Committee was informed that the Department had three wings, viz., Enforcement Wing, Drugs Testing Laboratory and Education in Pharmacy. At present, the sanctioned strength of the Department was 702 out of which 408 posts were filled. The Committee was apprised of the various challenges facing it, viz., inadequate staff for enforcement as well as for the laboratories.

4.4 The Committee was informed that a request had been made to Karnataka Public Service Commission for recruitment of 10 Drugs Inspectors and proposal had been submitted to the Government for creation of 430 posts, which included posts of Drugs Inspectors. Besides, there was need for adequate funds for construction of infrastructure and for procurement of necessary equipment/books.

4.5 From an analysis of the above facts, the Committee concludes that shortcomings witnessed in respect of coordination with and between the States as also in implementation of applicable legislations in the States are primarily an offshoot of inadequacies in manpower and infrastructure in the States. Strengthening the regulatory mechanism in the States will remain a far cry unless these infirmities are taken care of.

4.6 Given the lack of adequate resources in the States it would be unrealistic to expect them to improve the infrastructure and increase manpower without Central Assistance for strengthening drug control system. The Committee, therefore, recommends that the Ministry of Health and Family Welfare should work out a fully centrally sponsored scheme for the purpose so that the State Drug Regulatory Authorities do not continue to suffer from lack of infrastructure and manpower anymore. The Committee desires to be kept apprised of the initiatives taken by the Ministry in this regard.

4.7 It is a matter of grave concern that there are serious shortcomings in Centre-State coordination in the implementation of Drugs & Cosmetics Act and Rules. This, the Committee notes, is despite the Ministry's own admission that Section 33P of the Drugs and Cosmetics Act contains a provision that enables the Central Government to give such directions to any State Government as may appear to it to be necessary for implementation of any of the provisions of the Drugs and Cosmetics Act and Rules made thereunder. The Committee understands that these provisions are meant to be used sparingly. However, there have been several situations which warrant intervention through Rule 33 P. Therefore the committee hopes that in future the Ministry would not be found wanting in considering the option of using Section 33P to ensure that provisions of central drug acts are implemented uniformly in all states.

4.8 As regards lack of databank and accurate information, the Committee would like to observe that given the information technology resources currently

available, developing an effective system of coordination amongst State Drug Authorities for providing quality and accurate data could have been accomplished long back had the Ministry taken any initiative towards encouraging the States to establish a system of harmonized and inter-connected databanks. Evidently, no serious efforts seem to have been made in this regard. The Committee, however, expects that the Ministry would, at least now, play a more pro-active role in encouraging the States to employ modern information technology in the implementation of tasks assigned to them. At the same time a centralized databank (e.g. licenses issued, cancelled, list of sub-standard drugs, prosecutions etc.) may be created to which all the State Drug Authorities should be linked.

5. Capacity-building of Central and State Drug Testing Laboratories

5.1 The Committee was informed that the Central Drug Testing Laboratory, Hyderabad was yet to be equipped and the other five Central Drug Testing Laboratories at Kolkata, Mumbai, Chennai, Guwahati, and Chandigarh were reasonably equipped but not fully equipped and required upgradation with the state-of-the-art facilities for testing/analyzing complex formulations and detect spurious, misbranded, sub-standard and adulterated drugs. The Ministry has indicated that upgradation of the Central Drug Testing Laboratories would require 442 additional posts and augmentation of their infrastructure on a large scale. The present drug testing capacity of the six laboratories is 8,000 samples per annum, which is targeted to be increased to 24,000 samples per annum.

5.2 As per information furnished, there are 160 Drugs Testing Laboratories in the approved private and Government sectors in various states. The State Drugs Testing Laboratories test statutory samples from the Drugs Inspectors of the respective State Drugs Control Departments.

5.3 The Ministry informed the Committee that the private Drug Testing Laboratories test the samples on behalf of manufacturers who do not have their own testing and analysis facilities as the manufacturers are required to test the final product before releasing it into the market either at their own laboratory or private approved testing laboratory. These Drug Testing Laboratories are approved and monitored/inspected by the State Drug Authorities.

5.4 The State Governments or State Drug Authorities are expected to undertake the assessment of State Drugs Testing Laboratories with respect to the compliance of Good Laboratory Practices (GLP).

5.5 It has been admitted by the Ministry that the State Drugs Testing Laboratories are not fully equipped with adequate manpower and infrastructure.

5.6 The Committee, during the visit to Chennai undertook a visit to Central Drug Testing Laboratory and State Drug Testing Laboratory. The Central Laboratory has a total sanctioned staff of 33, out of which 29 were filled up and 4 vacancies were in the process of being filled up. The Committee was informed that this Laboratory needs a 5 storeyed building with 10,000 sq.ft., in each floor.

5.7 The Committee was informed that the Tamil Nadu Drugs Control Administration had a sanctioned strength of 337, out of which 203 were in position and 134 were vacant. The State testing laboratory was having only two HPLC systems bought more than a decade ago that had become obsolete. Hence there was a need for enhancement of facilities to keep up with the increased number of tests.

5.8 The Committee, during its visit to Chennai, also held discussions with the representatives of pharmaceutical industry. The representatives felt that there was need to provide more funds for upgradation of drug testing laboratories and more training for staff of Government Laboratory for proper analysis of samples. Other measures suggested by them included opening of 5 additional laboratories, need for more Appellant Laboratories in all zones in addition to the one located at Kolkata.

5.9 The representatives of the Ministry informed the Committee that the Government was planning upgradation of all Government Laboratories in the country and had proposed a massive investment in the Twelfth Plan proposals sent to the Planning Commission. As regards the issue of more appellate laboratories, the Ministry was examining the matter.

5.10 The Committee, during its visit to Bangalore, undertook a visit to Biocon Ltd., a pharmaceutical manufacturer. This in-house Testing Laboratory is approved by the Drug Authorities and tests samples from various plants belonging to the Biocon Group of Companies and also undertakes testing of samples upon customer request.

5.11 The Committee agrees that the capacity-building of the Central Drugs Testing Laboratories is the need of the hour. In this era of newer innovations coming up at rapid pace, equipping the Drug Testing Laboratories with the high-end sophisticated equipments is very essential. However, the Committee is aware that monitoring the quality of drugs is primarily the responsibility of the State Drugs Authorities, supplemented by CDSCO, which play a major role in collection of samples and testing them. Without manpower augmentation and upgradation of State Drugs Testing Laboratories, the objective of ensuring availability of quality drugs to the public cannot be realized. The Committee, therefore, recommends strengthening of both Central and State Drug Testing Laboratories.

6. Provision of requisite infrastructure at Airport and Seaport Offices

6.1 The CDSCO has eleven airport and seaport offices. During its visit to Chennai-Bangalore-Coonoor from 1 to 5 November, 2011, the Committee interacted with the authorities at Air Cargo Complex, Chennai to understand the systems and procedures followed by Assistant Drugs Controller's Office to facilitate processing of pharmaceutical imports and exports. Subsequently, Airports Authority of India, in a written submission, informed that the freight forwarders/shippers were required to bring the cargo requiring cold storage facility through refrigerated trucks only at Air Cargo complex to avoid spoilage of the contents of such cargo. The custodians at air cargo complexes were required to provide necessary infrastructure for the temperature sensitive cargo, at all stages, and ensure timely and proper handling of such cargo whilst in their custody. It was further stated that the role of the airlines was of paramount importance when the cargo stands released from the custodian and is to be uploaded to the connected flight. It was pointed out that the grey area was on the apron of the Airport where the incoming/outgoing cargo was often under the scorching sun for few hours by the airlines before loading of the same on their planes. It was suggested that the cooled dollies and thermal blankets could be pressed into service on the apron side by the airlines to provide requisite care to pharmaceutical products, thereby avoiding the deterioration/decay of the inside contents or potency of the vaccines/drugs/medicines etc.

6.2 The Committee agrees with the above suggestion and recommends that the Ministry of Health and Family Welfare should take initiative towards addressing the shortcomings forthwith in coordination with the Ministry of Civil Aviation at all seaports/airports handling import and exports of pharmaceutical products. The Committee will like to be informed of steps taken to address this problem.

7. New Drugs Approval

7.1 One of the most sensitive responsibilities of the CDSCO is to approve new drugs for marketing (both manufacture and import) in the country as empowered by and in compliance with Rule 122 and Schedule Y of the Drugs and Cosmetics Rules 1945.

7.2 The Committee was informed that currently the work involved in approval of New Drugs, including biologicals was being handled by 25 regular staff assisted by 25 contractual technical staff.

7.3 It was also stated that for smooth functioning of New Drugs Division, minimum additional staff required was three Deputy Drugs Controllers (I), 11 Assistant Drugs Controllers (I) and 31 Drugs Inspectors. One each of Biostatistician, Clinical Pharmacologist, Biochemist was also required, on a regular basis, for assisting in scrutiny of New Drugs applications. It was further stated that New Drugs Division was further required to be assisted by 12 Experts Committees to advise on various scientific issues of new drugs. For examination of applications of medical devices, at least, six Expert Committees were required. Apart from this, the New Drugs Division also required a state-of-the-art file storage system as it had voluminous technical data, a proper archival and retrieval system and creation of database in electronic format.

7.4 When asked as to the number of applications for import and manufacture of new drugs received by the New Drugs Division every year, and the time schedule prescribed for disposal of applications, it was stated that on an average (year 2005-2009), approximately, 1,600 applications of various categories of new drugs, including biologicals are received in a year.

7.5 These applications include New Drugs to be introduced for the first time in the country, subsequent applications of new drugs already approved by CDSCO, modified or new claims of approved drugs, namely, indications, dosage forms, etc., and new Fixed-Dose Combinations (FDCs) of two or more drugs.

7.6 It was stated that there are no statutory time lines prescribed for processing of new drug applications under Drugs and Cosmetics Act and Rules. The Committee was informed that the CDSCO had set 45 days as the deadline for the first response. No time schedule for final disposal is prescribed as it may vary from drug to drug (consultation with experts, if required, review of clinical trials etc.) and adequacy of the data furnished by the applicant.

7.7 The Committee was informed that there was no permanent panel of medical experts attached with the CDSCO. However, two Expert Committees, namely, Investigational New Drug (IND) Committee and Cellular Biology-based Therapeutic Drug Evaluation Committee had been set up by the Ministry of Health and Family Welfare for advice to DCG (I). Apart from this, experts from subject specialties are identified from time to time amongst the medical specialists from institutes like PGI, Chandigarh; AIIMS; ICMR; KEM Hospital, Mumbai; CMC, Vellore, etc., as well as individual practicing clinicians for their expert opinion.

7.8 Explaining about the different stages of approval of new drugs, the Ministry stated that applications of new drugs are examined as per provisions of Schedule Y of Drugs and Cosmetics Rules. The different stages of approval of new drugs, including vaccines, are as under:

- Examination of the application in respect of the following documents:
 - Application in Form 44, i.e. Fee and Chemistry-Manufacturing-Control (CMC) data;
 - Data submitted in respect of chemical, toxicological, pharmacological, clinical and other documents.
- In case of incomplete application, the applicant is asked to provide requisite data;
- Examination of the complete data as submitted by the firm;
- Consultation of the expert, wherever considered necessary;

- Testing of sample of new drugs (bulk/imported formulation) at Central Drugs Laboratories;
- Review of the essentiality of clinical trial in the country;
- In case clinical trial is considered necessary, the applicant is requested to furnish clinical trial protocol. However, for drugs indicated in life threatening/serious disease, or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirement may be abbreviated, deferred or omitted;
- If protocols of clinical trial are found in order, permission for clinical trial is granted;
- Clinical trial reports submitted by the firm after completion of the trial are examined and, if required, opinion of the experts is solicited;
- The applicant may then be asked for technical presentation on the drugs;
- If the application is complete in all respects, permission/approval is granted;
- In case of Investigational New Drug, the proposal, starting from the clinical trial application stage, is referred to IND Committee and decision to approve or otherwise is taken as per recommendation of the Committee.

7.9 The Ministry further stated that in order to ensure the adherence to the guidelines and regulatory requirements, the new drugs applications are examined /reviewed, through a channel of submissions as follows:

Technical Data Associates/ Technical Officer/Drugs Inspectors/ Asstt. Drugs Controller (I) /Dy. Drugs Controller (I) /DCGI.

7.10 Briefly the statutory rules require that apart from submitting specified documentation (pharmacology, toxicology, animal studies, overseas clinical trials etc.), the applicant for New Drugs discovered outside India should conduct Phase-III trials on not less than 100 patients at 3-4 different hospitals in India to test the efficacy and safety of new drugs for proposed indication(s). The basic purpose of Phase III trials is to determine if there are any ethnic differences that can alter the metabolism, efficacy and safety of the drug when administered to patients of different ethnicities living in India (such as Indo-Aryans, Dravidians, Mongoloids,

Tribals etc.). There is evidence that the effect of some drugs can vary among various ethnic groups. For example, the blood levels reached after intake of lipid lowering agent rosuvastatin are far higher in Asians, compared to Europeans and North American Caucasians, Hispanics and Blacks needing lowering of dosage. Failure to lower dose in Indians can result in severe toxicity, including life-threatening muscle injury leading to fatalities. Hence, testing drugs in the Indian ethnic groups is of paramount importance before approving any drug of foreign origin.

7.11 In order to scrutinize new drug approvals, the Committee sought details [sponsors; pre-approval Phase III clinical trials; overseas regulatory status in US, Canada, Britain, Australia and European Union; indications; names of experts if consulted and Post-Marketing Safety Update Reports (PSURs)] in respect of randomly selected 42 medicines from the list of new drugs uploaded by CDSCO on its website. Of these, 38 drugs were approved in the years 2004 to August 31, 2010; one drug had been approved earlier in 2001. Three drugs had been approved earlier in mid 90s. In all DCGI had approved 2,167 drugs in the period January 2001 to 30-11-2010. Thus the sample size for random scrutiny was less than 2 percent.

7.12 Out of 42 drugs picked up randomly for scrutiny, the Ministry could not provide any documents on three drugs (pefloxacin, lomefloxacin and sparfloxacin) on the grounds that files were non-traceable. All these drugs had been approved on different dates and different years creating doubt if disappearance was accidental. Strangely, all these cases also happened to be controversial drugs; one was never marketed in US, Canada, Britain, Australia and other countries with well developed regulatory systems while the other two were discontinued later on. In India, all the three drugs are currently being sold. It is not possible to monitor if manufacturers are abiding by the conditions of approval viz. indications, dosage, contra-indications, precautions etc. Updation of product monographs and safety information in the light of recent developments is also not possible putting patients at risk. Before being withdrawn, major changes in safety profile, including Black Box Warnings (meant to draw attention to serious side effects), were incorporated to the prescribing guidelines of the two drugs sold in the United States but later withdrawn from the market.

7.13 The Committee is of the view that due to untraceable files on three drugs, it is not possible to determine if all conditions of approval (indications, dosage, safety precautions) are being followed or not. Moreover the product monographs cannot be updated in the light of recent developments and regulatory changes overseas. Therefore all the missing files should be re-constructed, reviewed and monographs updated at the earliest.

7.14 On scrutiny of 39 drugs on which information was available, the Committee found the following shortcomings:

- In the case of 11 drugs (28%) Phase III clinical trials mandated by Rules were not conducted. These drugs are i, Everolimus (Novartis), ii. Colistimethate (Cipla), iii. Exemestane (Pharmacia), iv. Buclizine (UCB), v. Pemetrexid (Eli Lilly), vi. Aliskiren (Novartis), vii. Pentosan (West Coast), viii. Ambrisentan (GlaxoSmithKline), ix. Ademetionine (Akums), x. Pirfenidone (Cipla), and xi. FDC of Pregabalin, Methylcobalamine, Alpha Lipoic Acid, Pyridoxine & Folic Acid (Theon);
- In the case of 2 drugs (Dronedarone of Sanofi and Aliskiran of Novartis), clinical trials were conducted on just 21 and 46 patients respectively as against the statutory requirement of at least 100 patients;
- In one case (Irsogladine of Macleods), trials were conducted at just two hospitals as against legal requirement of 3-4 sites;
- In the case of 4 drugs (10%) (Everolimus of Novartis; Buclizine of UCB; Pemetexid of Eli Lilly and FDC of Pregabalin with other agents), not only mandatory Phase III clinical trials were not conducted but even the opinion of experts was not sought. The decision to approve these drugs was taken solely by the non-medical staff of CDSCO on their own.
- Of the cases scrutinized, there were 13 drugs (33%) which did not have permission for sale in any of the major developed countries (United States, Canada, Britain, European Union nations and Australia). None of these drugs have any special or specific relevance to the medical needs of India. These drugs are: i. Buclizine for appetite stimulation (UCB); ii. Nimesulide injection (Panacea); iii. Doxofylline (Mars) iv. FDC of Nimesulide with Levocetirizine (Panacea); v. FDC of Pregabalin with other agents (Theon); vi. FDC of Tolperisone with Paracetamol (Themis); vii. FDC of Etodolac with

Paracetamol (FDC); viii. FDC of Aceclofenac with Thiocolchicoside (Ravenbhel); ix. FDC of Ofloxacin with Ornidazole (Venus), x. FDC of Aceclofenac with Drotaverine (Themis); xi. FDC of Glucosamine with Ibuprofen (Centaur); xii. FDC of Diclofenac with Serratiopeptidase (Emcure) and xiii. FDC of Gemifloxacin with Ambroxol (Hetero).

- In the case of 25 drugs (64%), opinion of medically qualified experts was not obtained before approval.
- In those cases (14 out of 39 drugs), where expert opinion was sought, the number of experts consulted was generally 3 to 4, though in isolated cases the number was more. In a country where some 700,000 doctors of modern medicine are in practice such a miniscule number of opinions are hardly adequate to get diverse views and come to a well considered rational decision apart from the possibility of manipulation by interested parties. As against this, to review just the dose of popular pain-killer paracetamol, the United States Food and Drug Administration (USFDA) constituted a panel of 37 experts drawn from all over the country. After extensive debate 20 members sought ban on the combination of paracetamol with narcotics (17 opposed), 24 members sought reduction of dose from 500mg to 325mg (13 opposed) and 26 members advised to make high dose (1000mg) formulation a prescription only medicine (11 opposed). The voting pattern shows independent application of mind by each member. The opinions and decisions are in public domain (website of USFDA) so that anyone is free to scrutinize, offer comments and give suggestions. In India, every discussion and document is confidential away from public scrutiny. **This matter needs to be reviewed to ensure safety of patients, fair play, transparency and accountability.**

7.15 Unless there is some legal hitch, the Committee is of the view that there is no justification in withholding opinions of experts on matters that affect the safety of patients from public. Consideration should be given to upload all opinions on CDSCO website.

7.16 According to information provided by the Ministry, a total of 31 new drugs were approved in the period January 2008 to October 2010 without conducting clinical trials on Indian patients. The figure is understated because two drugs

(ademetonine and FDC of pregabalin with other ingredients) were somehow not included in the list. Thus there is no scientific evidence to show that these 33 drugs are really effective and safe in Indian patients.

7.17 The Ministry explained that under the rules, DCGI has the power to approve drugs without clinical trials in “Public Interest.” No explanation is available as to what constitutes Public Interest. How can approvals given to foreign drugs without testing on Indians be in Public Interest? Some of the reasons given for irregular approvals are: “Serious disease” (all the more reason to conduct clinical trials to ensure that patients in India really benefit from such imported, exorbitantly expensive drugs), “Rare disease status according to United States Food and Drugs Administration” (How can USFDA decide which is rare disease in India?), “Orphan drug status in Europe and USA” (There is no provision in Indian laws to give special treatment to such foreign drugs).

7.18 When asked about the reasons for approving New Drugs without clinical trials, the Health Secretary, during the course of oral evidence, stated that approval of new drugs without Phase-III clinical trials in “public interest” was being done with the support of technical advice. Explaining about the basis for deciding to waive off the condition of local clinical trials for manufacture/import of new drugs, the Ministry stated that the Drugs and Cosmetics Rules do not prescribe specific situation under which clinical trial exemption can be granted due to “public interest”. However, the DCGI can abbreviate, defer or omit the toxicological and clinical data requirements for drugs meant for life-threatening/serious diseases and diseases of special relevance to Indian health scenario. It was further claimed that in such cases status of regulatory approval of the said drug in other countries and opinion from the medical specialists of the relevant field is obtained for taking decision. Further, the marketing approval is conditional to applicants submitting post-marketing surveillance data.

7.19 In cases where foreign drugs were approved without clinical trials in the country, the Ministry offered the following explanation: *“Most of the drugs are approved in other countries based on multinational clinical trials.... on various ethnic/racial populations”* implying that Indians would be included and hence conducting trials in India was not necessary. However, this presumptive remark is not accompanied by

any evidence. The interest is in those ethnicities that live in India, not Slavs, Caucasians, Hispanics and Negroes. The information in the Status Note on the very first drug of a total of 31 in the list of new drugs permitted in “public interest” without clinical trials, daptomycin, shows that pre-approval studies conducted by the American innovator recruited just 558 patients in United States, South Africa, Europe, Australia and Israel. There is absolutely no evidence of major ethnic groups of India being enrolled in these small trials.

7.20 It would appear that the intention of those who framed the Act and Rules was to leave a small door ajar for entry of new drugs without undergoing trials in serious emergency situations such as epidemic of a new hitherto unknown disease (e. g. SAARS, Bird Flu or Swine flu) where there may not be time enough to test new drugs and there is no alternative but to take calculated risk. None of the 33 drugs fall in this category of emergency treatments. Besides many drugs were launched in overseas markets years ago with ample time to conduct trials in India. The following are some examples:

- Daptomycin (Cubicin) of Novartis was launched overseas on 13-9-2003 and approved in India on 28-1-2008 after a gap of over four years. There was no tearing hurry to approve the drug without trials.
- Pemetrexed (Alimta) of Eli Lilly was approved on 5-2-2004 in the United States. After a gap of more than two years, it was approved by DCGI on 28-6-2006 without trials. There was more than adequate time to conduct Phase III trials in India and yet undue favour was shown to the manufacturer.
- Raltegravir (Isentress) of Merk Sharp and Dhome was launched abroad on 12-10-2007 and approved in India on 27-01-2010 without conducting clinical trials even though there was adequate time to conduct mandatory clinical trials.

7.21 Such irregular approvals spare drug producers the cost and efforts but put Indian patients at risk. On an average DCGI is approving one drug every month without trials. This cannot be in public interest by any stretch of imagination. Moreover it was stated that in such cases (i) expert opinion is sought and (ii) Post-Marketing Surveillance Data is mandatory.

- However a look at the information on approvals given by DCGI shows that expert opinion was sought in only 5 of 33 such out-of-the-way approvals.
- With regard to Post-Marketing Surveillance data, the Ministry failed to provide even one out of randomly selected 4 drugs approved without trials.

7.22 As stated earlier, the very purpose of Phase III trials is to determine any ethnic/racial differences in the safety, efficacy and metabolism of drugs. Hence to serve any useful purpose, patients of different ethnicities living in India should be enrolled. For example, the results of a trial conducted only on Indo-Aryans may not be applicable to Mongoloids or Dravidians due to genetic differences.

7.23 In response to a question as to how various ethnic groups are being enrolled in Phase III clinical trials, the Committee was informed that *“most trials were taking place in cosmopolitan towns. It is understood that cosmopolitan cities have a heterogeneous population comprising various ethnic groups. Otherwise there is no proactive, specific procedure to test new drugs on different ethnic groups.”*

7.24 However, a scrutiny of randomly selected trial sites shows that the Ministry’s submission is incorrect and the basic purpose of Phase III trials, even when conducted, is not being served. The following are some illustrative examples:

- A trial (rifaximin) took place at Kota, Jaipur and Mumbai. Kota and Jaipur can hardly be classified cosmopolitan in demography.
- Another trial (doxofylline) took place just in Hyderabad and Aurangabad. Aurangabad certainly is not a cosmopolitan city.
- Sites of another trial (ramosetran) were limited to Betul, Indore and Bhopal (all in Madhya Pradesh) and Vadodara (Gujarat). None of them is a cosmopolitan town.
- Trial on FDC of etodolac with paracetamol was conducted just in Maharashtra (Nagpur, Pune and Mumbai).
- Trials on another FDC of aceclofenac with drotaverine were conducted only in Maharashtra (Aurangabad, Pune and Mumbai).
- In the case of FDC of diclofenac with serratiopeptidase (India being the sole country in the world to have approved such a combination),

though trials were held at 8 sites but 6 of them were in Pune alone and 2 in Mumbai; all of them by private practitioners.

7.25 Even if a handful of individuals of different ethnic origins were residing in the towns/cities listed above, the chances of their being patients and then recruitment into clinical trials were remote.

7.26 On the other hand an analysis of 164 randomly selected sites of pre-approval drug trials shows that only one site was located in Guwahati, where one can find adequate number of patients of Mongoloid origin since many of them also come from other North East states for treatment.

7.27 It is obvious that DCGI clears sites of pre-approval trials without application of mind to ensure that major ethnic groups are enrolled in trials to have any meaningful data. Thus such trials do not produce any useful data and merely serve to complete the formality of documentation.

7.28 The Committee recommends that while approving Phase III clinical trials, the DCGI should ensure that subject to availability of facilities, such trials are spread across the country so as to cover patients from major ethnic backgrounds and ensure a truly representative sample. Besides, trials should be conducted in well equipped medical colleges and large hospitals with round the clock emergency services to handle unexpected serious side effects and with expertise in research and not in private clinics given the presence of well equipped medical colleges and hospitals in most parts of the country in present times.

7.29 The Committee is of the view that taking into account the size of our population and the enormous diversity of ethnic groups there is an urgent need to increase the minimum number of subjects that ought to be included in Phase III pre-approval clinical trials to determine safety and efficacy of New Drugs before marketing permission is granted. In most western countries the required numbers run into thousands. However since the major objective in India is to determine the applicability or otherwise of the data generated overseas to Indian population, the requirement should be re-assessed and revised as per principles of medical statistics so that major ethnic groups are covered. A corresponding increase in the number of sites so as to ensure a truly representative sample spread should also be laid down in black and white. Furthermore, it should be ensured that sites

selected for clinical trials are able to enroll diverse ethnic groups. For domestically discovered drugs, the number of subjects should be revised as well. This can be easily achieved by changes in the Good Clinical Practice (GCP) guidelines.

7.30 The Committee was informed that while taking decision on new drugs opinion of independent experts is obtained whenever considered necessary by CDSCO. The Committee scrutinized some random cases to assess the credibility and utility of such opinions.

7.31 A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data. Such opinions are of extremely limited value and merely a formality. Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures. The Committee observed the following facts on scrutiny of opinions:

- In the case of clevudine (of Phamasset Inc.), three experts (a Professor of Medicine of All India Institute of Medical Sciences, New Delhi; a Professor of Medicine of K. B. N. Medical College, Gulbarga; a Professor of Medicine of R. G. Kar Medical College, Kolkata) located at different places thousands of miles apart from each other sent word to word identical letters of recommendation. In addition all of them went out of the way and gave unsolicited advice, in identical language, to the DCGI to give permission to the company to market the drug without conducting mandatory clinical trials in India (**Annexure 1**).
- In case of sertindole (Serdolect of Lundbeck), an anti-psychotic drug, three experts located at three different places (a Professor and Head of the Department of Psychiatry of Stanley Medical College, Chennai; Professor of SKP Psychiatric Nursing Home, Ahmedabad and a Professor and Head of the Department of Psychiatry of LTM Medical College, Mumbai) wrote letters of recommendation in nearly word-to-word, identical language and not surprisingly all of them used the incorrect full form of DCGI in the address! Is such a coincidence possible unless the person behind the scene who actually drafted the letters is one and the same person? (**Annexure 2**).

- In the case of doxofylline, an anti-asthmatic, two opinions (from Professor of Medicine of M. G. M. Medical College, Indore and Consultant, Indraprastha Apollo Hospital, New Delhi) are exactly, word-to-word identical. **(Annexure 3).**
- The three opinions (from Professor of Orthopaedics, All India Institute of Medical Sciences, New Delhi; Consultant at Dayanand Medical College, Ludhiana and Professor of Orthopaedics, St. Johns Medical College, Bangalore) on rivaroxaban (Bayer) a drug for prevention of clotting are merely ditto copies of each other. **(Annexure 4).**
- In case of ademetionine, all four letters of recommendation (from Professor of the Department of Gastroenterology, Lokmanya Tilak Medical College, Mumbai and Professor of Gastroenterology, Medical College, Thiruvananthapuram; Professor and Head of the Digestive and Liver Diseases, IPGMER, Kolkata; Chairman and Chief of Hepatology Services, Sir Ganga Ram Hospital, New Delhi) made similar comments; three out of four letters are undated (is it merely a coincidence?) while one is dated 11-8-2010. The letter from Asst. Drugs Controller (India) seeking expert opinion is dated 9-8-2010. It is amazing that letter dated 9th August 2010 from New Delhi not only reached Mumbai on 11th August 2010 but was replied the very same day, that too, after reviewing 131 of pages of scientific papers. All the four letters are addressed incorrectly though identically to “Directorate General of Health Services” without any address and without even a PIN code. None of the letters were diarized by the office of the Drugs Controller General (India) when received. The drug was approved on 1-9-2010 without Phase III clinical trials. **(Annexure 5).**
- Letters of opinion recommending approval for pirfenidone of Cipla from Professor of Pulmonary Medicine, AIIMS, New Delhi dated 19th June, 2010, Consultant Chest Physician, Lilavati Hospital, Mumbai dated May 25, 2010; Additional Professor of Pulmonary Medicine, PGI, Chandigarh dated 14th June, 2010; Pulmonologist of Yashoda Hospital, Secunderabad dated 12th June 2010 were all received exactly on the same day 2-7-2010 and diarized by DCGI office under consecutive references 4877, 4878, 4879 and 4880. **Is the Committee mistaken in coming to the conclusion that all**

these letters were collected by interested party from New Delhi, Mumbai, Chandigarh and Secunderabad and handed over to office of the DCGI on the same day? If so, it is obvious that the interested party was in the loop in the entire process of consultation with experts. (Annexure 6).

- Letters of opinion recommending approval of dapoxetine from Professor and Head, Department of Urology, T. N. Medical College, Mumbai dated 25-3-2010; Professor and Head, Department of Psychiatry, L. T. M. Medical College, Mumbai dated 19-3-2010; Professor and Head, Department of Urology, Calcutta National Medical College, Kolkata dated 24-2-2010 all reached the office of DCGI exactly on the same date 6th April 2010 and were diarized under consecutive references 3667, 3668 and 3669. It is surprising that letter dated 24-2-2010 from Kolkata took more than six weeks to reach Delhi. Is it unreasonable on the part of the Committee to come to the conclusion that all these letters were collected by interested party from New Delhi, Mumbai and Kolkata and delivered to the office of DCGI on the same day? (Annexure 7).
- Letters of opinion recommending approval of nimesulide injection from Professor and Head, Department of Medicine, Government Medical College, Aurangabad dated 17-8-2005 and Sr. Consultant Orthopaedic Surgeon, Indraprastha Apollo Hospital, New Delhi dated 17-6-2005 reached exactly on the same day i.e. 23-8-2005 and were diarized under consecutive reference 3537 and 3538. **It is inconceivable that a letter dated 17-6-2005 from New Delhi will be delivered to the office of DCGI also in New Delhi after more than two months. The conclusion, as in aforementioned cases, is obvious. (Annexure 8).**

7.32 If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more outrageous than clinical trial approval given to the Fixed Dose Combination of aceclofenac with drotaverine which is not permitted in any developed country of North America, Europe or Australasia. In this case, vide his letter number 12-298/06-DC dated 12-2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not

only to select experts but get their opinions and deliver them to the office of DCGI! No wonder that many experts gave letters of recommendation in identical language apparently drafted by the interested drug manufacturer. These experts include:

- i. Professor & Head, Department of Pharmacology, PGI, Chandigarh.
- ii. Professor & Head, Department of Pharmacology & Clinical Pharmacology, Christian Medical College, Vellore.
- iii. Professor of Surgery, L. T. M. Medical College, Mumbai.
- iv. Professor of Medicine, Gandhi Medical College, Secunderabad.
- v. Professor and Head of Postgraduate Department of Surgery, S. C. B. Medical College, Cuttack.
- vi. Professor of Medicine and Civil Surgeon, Gandhi Medical College, Secunderabad. (Annexure 9).

7.33 In the above case, the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug.

7.34 Such expert opinions in identical language and/or submitted on the same day raise one question: Are the experts really selected by the staff of CDSCO as mentioned in written submission by the Ministry? If so how can they, situated thousands of miles away from each other, draft identically worded letters of recommendation? Is it not reasonable to conclude the names of experts to be consulted are actually suggested by the relevant drug manufacturers? It has been admitted that CDSCO does not have a data bank on experts, that there are no guidelines on how experts should be identified and approached for opinion.

7.35 The Committee is of the view that many actions by experts listed above are clearly unethical and may be in violation of the Code of Ethics of the Medical Council of India applicable to doctors. Hence the matter should be referred to MCI for necessary follow up and action. In addition, in the case of government-employed doctors, the matter must also be taken up with medical colleges/hospital authorities for suitable action.

7.36 There is sufficient evidence on record to conclude that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts.

7.37 On a more fundamental issue the Committee has come to the conclusion that when it comes to approving new drugs, too much is left to the absolute discretion of the CDSCO officials. There are no well laid down guidelines for determining whether consultation with experts is required. Thus the decision to seek or not to seek expert opinion on new drugs lies exclusively with the non-medical functionaries of CDSCO leaving the doors wide open to the risk of irrational and incorrect decisions with potential to harm public health apart from the possibility of abuse of arbitrary discretionary powers.

7.38 The Committee, therefore, strongly recommends that there should be non-discretionary, well laid down, written guidelines on the selection process of outside experts with emphasis on expertise including published research, in the specific therapeutic area or drug or class of drugs. Currently, the experts are arbitrarily chosen mainly based on their hierarchical position which does not necessarily correspond to the area or level of expertise. All experts must be made to file the Conflict of Interest declaration outlining all past and present pecuniary relationships with entities that may benefit from the recommendations given by such experts. The consulted experts should be requested to give hard evidence in support of their recommendations.

7.39 There has been extensive adverse media coverage with allegations that many drugs have been approved unlawfully. The Committee sought comments from the Ministry on some selected cases and based on the information received and other documented sources has come to the following conclusion:

Buclizine (applicant: UCB, Belgium) was approved on 28-6-2006 for appetite stimulation without clinical trials and without consulting experts for use in children. Under the law of the land if an old drug approved for a disorder (such as allergy) is to be used for another indication (such as appetite stimulation), then it is deemed to be a New Drug and must undergo the entire procedure applicable to New Drugs and meet all regulatory requirements. In response to the questionnaire from the Committee, the Ministry gave incorrect and misleading information. When asked whether the drug is approved in the US, Canada, Britain, European Union and Australia, instead of saying "Yes" or "No" answer to each of the specified countries, the Ministry went out of the way to volunteer incorrect information that it was approved in "Belgium, Brazil, Luxemburg, Bolivia, South Korea, Venezuela,

Malaysia and others.” Firstly, regulatory status in developing countries such as Bolivia, Venezuela, Malaysia is not of much help in determining the safety and efficacy of a drug [according to a survey done by the World Health Organization (WHO), only about half of 192 member states have drug controllers]. Secondly, the Company’s own Core Data Sheet (detailed product information document) issued from its headquarters in Belgium says: *“Because of lack of approved clinical studies and scientific data, the benefit/risk is negative for the indication of buclizine for appetite stimulation.”* Thus, buclizine is not currently approved in Belgium, the innovator country, for appetite stimulation. The correct status in other countries, even for use in allergy, is as follows:

- Brazil (discontinued for all indications),
- Bolivia (authorization not renewed in December, 2003 for all indications),
- Luxemburg (not permitted to be used as appetite stimulant);
- Malaysia (discontinued for all indications);
- South Korea (banned).

7.40 The Core Data Sheet is on record in the CDSCO files. Buclizine is just one of the many drugs that have been approved in violation of the Indian laws.

7.41 The Committee is of the view that responsibility needs to be fixed for unlawfully approving Buclizine, a drug of hardly any consequence to public health in India, more so since it is being administered to babies/children. At the same time the approval granted should be reviewed in the light of latest scientific evidence, regulatory status in developed countries, particularly in Belgium, the country of its origin.

7.42 **Letrozole** discovered by Novartis, is an anti-cancer drug for use only in post-menopausal women and is contraindicated (not permitted) to be used in women of reproductive age. If it is to be used for any other indication except breast cancer, then the drug is categorized as a New Drug under Indian laws. On 10-04-2007, DCGI approved the use of letrozole for improving female fertility. The Drugs and Cosmetic Rules require that while approving a drug for use in females of reproductive age, animal studies are to be done in this specific group. No such studies were done in India. The innovator also did not conduct such studies abroad

because there was no plan to use letrozole in women of reproductive age. Under Indian rules, Phase II studies should have been conducted before Phase III since such studies were not conducted anywhere. Permission to conduct Phase III studies was given without prior Phase II studies. Phase III clinical trial was conducted on just 55 women by three doctors in private practice while the minimum requirement as per mandatory Good Clinical Practice (GCP) rules is at least 100. After approval, the sponsor, Sun Pharmaceuticals did not submit periodic PSURs due every six months as required by law. No action was taken against the Company in such a sensitive case since India is the only country where the drug is permitted to be used for female infertility. Post-marketing data is crucial and critical in detecting adverse effects both in women and babies born to them if they use letrozole before the onset of pregnancy. Clearly there was a serious lapse on the part of CDSCO. In the wake of media outcry, in a diversionary move, the DCGI instead of investigating the allegations of regulatory lapse and taking corrective measures referred the matter to clinical experts, DTAB etc. on the restricted issue of safety and efficacy. **DCGI is expected to take action against those CDSCO functionaries who colluded with private interests and got the drug approved in violation of laws. The drug has since been banned by the Ministry for use in female infertility.**

7.43 The Committee takes special note of this case of gross violation of the laws of the land by the CDSCO. First, in approving the drug for use in case of female infertility and thereafter, in exhibiting overt resistance in taking timely corrective steps despite very strong reasons favouring immediate suspension of use of letrozole for the said indication. Belatedly, the drug has been banned for use in female infertility.

7.44 FDC of flupenthixol and melitracen (Deanxit): Except for giving file number (12-62/95-DC) and the date of approval (28-10-1998), the Ministry failed to provide any documents and information on the regulatory process that led to its approval (such as import permission, mandatory clinical trials etc.). The combination contains two drugs, flupenthixol and melitracen. Melitracen has never been approved and used in India. Therefore under Schedule Y, Appendix VI (a), the combination is a “New Drug” for two reasons (i) because one of the two ingredients has not been approved in the past and (ii) because all combinations (FDCs) are classified as New Drugs. CDSCO violated the rules by approving the drug on following counts;

- Drugs and Cosmetic Rule 30-B bans the import and marketing of any drug the use of which is prohibited in the country of origin. Deanxit was and continues to be prohibited for sale and use in Denmark, its country of origin. Therefore permission to import and market was given unlawfully.
- Since Melitracen was not individually approved earlier, the Combination had to undergo all phases of development (Phase I, II and III). Permission to conduct the last phase III, if given was in violation of rules.
- Before approving the indications of a New Drug, it is mandatory to conduct clinical trials individually for all the different indications. A perusal of the Marketing Approval dated 28th October 1998 shows that the approved indications were: (i) Psychogenic depression, (ii) Depressive neuroses, (iii) Masked depression and (iv) Psychosomatic affections accompanied by anxiety and apathy. In its submission the Ministry failed to give details of trials at 3-4 sites with at least 100 patients for each indication as required by law. As per the package insert on Deanxit, the brand is being indicated and promoted for two unapproved indications i.e. "Menopausal depression", "Dysphoria and depression in alcoholics and drug addicts." (**Annexure 10**). The approval letter issued to the sponsor clearly states at serial number 7: *"No claims except those mentioned above shall be made for this drug without the prior approval of this Directorate (DCGI).*

7.45 The Committee is of the opinion that there must be some very good reasons for Danish Medicine Agency (Denmark) not to approve a domestically developed drug where an anti-depressant drug would perhaps be in greater demand as compared to India. Curiously, Deanxit is allowed to be produced and exported but not allowed to be used in Denmark.

7.46 The Committee feels that the DCGI should have gone into the reasons for not marketing the drug in major developed countries such as United States, Britain, Ireland, Canada, Japan, Australia just to mention a few. United States alone accounts for half of the global drug market. It is strange that the manufacturer is concentrating on tiny markets in unregulated or poorly regulated developing countries like Aruba, Bangladesh, Cyprus, Jordan, Kenya, Myanmar, Pakistan, and Trinidad instead of countries with far more patients and profits. Many of these developing countries are handicapped due to lack of competent drug regulatory authorities. Instead of examining and reversing regulatory lapses,

DCGI has referred the matter to an Expert Committee to look at the isolated and restricted issue of “safety and efficacy” instead of unlawful approval in the first place.

7.47 The approval of this drug is in clear violation of the Drugs and Cosmetics Rules. As per Rules, a New Drug is deemed to be a New Drug for four years. After four years, the State Drug Authorities have the powers to issue manufacturing licenses without reference to DCGI. Therefore, if initial approval is given unlawfully by the DCGI, the doors open for other manufacturers to market the drug after four years. This is exactly the situation with FDC of flupenthixole and melitracen. **The Committee recommends that in view of the unlawful approval granted to Deanxit, the matter should be re-visited and re-examined keeping in mind the regulatory status in well developed countries like Denmark, the country of origin; the United States, Britain, Canada, European Union and Japan etc. It is important to keep in mind that in Europe, there are two types of marketing approvals: Community-wide (cleared by European Medicine Agency) and individual regulators of member nations. EMEA is known to clear drugs after great deal of scrutiny while the competence and expertise of drug regulatory authorities of individual nations is not uniform and varies greatly from country to country.**

7.48 Placenta Extract: As per Drugs and Cosmetics Rules, whenever there is either an additional formulation (such as tablets, solutions, suspensions, injections, controlled release, gels etc.) or proposal to use in additional indications, the drug is deemed to be a ‘New Drug’. In violation of this clear rule, vide its letter number 4-97/89-DC dated 11th February 2000, an official of the office of the Drugs Controller General (India) wrote a letter to the manufacturer that Placenta Extract was “*not a New Drug*’ and gave permission to promote placenta extract *gel* [a new formulation and hence classified as a New Drug as per Rule 122.E(b)] in additional indications (Burns and Wounds, Non-Healing Indolent Ulcers, Bed Sores, Mucositis etc.). By including the term “*etc.*” (An unknown and unheard of terminology in the history of drug approval), loopholes were left wide open to add other indications. Thus CDSCO went out of the way to unlawfully and wrongly certify, in black and white, that the drug was “*not a New Drug*” thus helping the manufacturer to market an additional formulation for additional indications.

The manufacturer's letter dated 7th February 2000 from Kolkata reached CDSCO in Delhi and was processed with super speed in a record time of just 4 days (inclusive of postal transit) and permission granted on 11th February 2000 (**Annexure 11**). Since then the Delhi High Court has reduced the approved indications to just two disorders: Wound Healing (for topical gel) and Pelvic Inflammatory Disorder (for injection).

7.49 The Committee recommends an enquiry into the said letter. The responsibility should be fixed and appropriate action taken against the guilty. The Committee should be kept informed on this case.

7.50 Nimesulide for use in children: The drug was approved in 1996 for use in children of all age groups (from Day 0 to 12 years) without conducting any clinical trials in India. Following some deaths due to liver injury in Europe, the drug was banned all over the world for use in children nearly 7 years ago. There was extensive media coverage in India. Instead of addressing the concern on regulatory lapse the matter was referred to an Experts Committee of DTAB to examine the "efficacy and safety issues." Since the drug has been banned on 10-2-2011 for use in children, the matter is being mentioned in this report as a matter of record.

7.51 The Committee takes special notice of this case of persistent insolence on the part of CDSCO and hopes that never again shall the DCGI approve drugs in violation of laws, that too for use in neonates and young children.

7.52 The Committee expresses its deep concern, extreme displeasure and disappointment at the state of affairs as outlined above. The Ministry should ensure that the staff at CDSCO does not indulge in irregularities in approval process of new drugs that can potentially have adverse effect on the lives of people. It is difficult to believe that these irregularities on the part of CDSCO were merely due to oversight or unintentional. Hence all the cases listed above and cases similar to these should be investigated and responsibility fixed and action taken against erring officials whether currently in service or retired.

8. Drugs withdrawn/discarded/banned abroad.

8.1 There has been lot of public concern on the continued availability of potentially harmful drugs in India years after such products were banned and/or withdrawn

abroad, more particularly in highly developed countries like United States, Canada, Britain, European Union, Australia etc. For example anti-diabetic agent phenformin due to unacceptable side effects and introduction of safer medicines was banned abroad in 70s but continued to be sold in India till 2003 i.e. for over 30 years, that too when Delhi High Court raised the issue.

8.2 The Committee had initially decided to examine all the controversial drugs. However in the recent past, though belatedly, the Central Government has banned five of them. Therefore, only few drugs are being taken up for consideration as illustrations.

Analgin remained in the market worldwide until the 1970s, when it was found that the drug carried risk of causing severe fall of white cells (agranulocytosis) - a potentially fatal condition. The global status of ban orders, based on information from WHO is as follows: (Countries where analgin was never approved are not listed.)

United States: banned with effect from June 27, 1977. Analgin was also banned for use in animals in 1995 in the United States.

Sweden: banned in 1997 due to reports of agranulocytosis in Sweden.

France 2006: Analgin withdrawn due to negative benefit/risk evaluation.

Armenia: banned in February 2000 by the Drug and Medical Technology Agency.

Morocco banned in May 2000 on the recommendation of the National Advisory Commission for Pharmacovigilance following an official survey which showed severe adverse reactions associated with this product.

Syria: The Suprim Technical Committee and the Ministry of Health banned the manufacture of analgin in 1996.

Yemen: In 1998, the Supreme Board of Drugs and Medical Appliances banned analgin because of its potential to cause anaphylactic shock and agranulocytosis.

Zimbabwe: In 1998: The Medicines Control Authority cancelled the registration of analgin due to the potential risks.

Lithuania: In September 2000, the marketing authorization for tablets was not renewed for safety reasons.

Democratic Republic of Timor-Leste 2005: Analgin to be removed due to reports of agranulocytosis.

Nigeria 2005: In view of recorded cases of adverse reactions the National Agency for Food and Drug Administration & Control (NAFDAC) ordered that with effect from 1st January, 2006, the sale and use of analgin drugs are banned.

Serbia May 2005: Prohibited the use of analgin in children and adolescents under the age of 18 years.

Philippines June 2009: Analgin banned.

The drug is also banned in **Nepal, Vietnam, Canada, Australia, New Zealand, Japan and Iran.**

8.3 There are some specific problems in India with regard to rampant use of pain-killers without medical advice. Analgin is an NSAID but virtually sold as Over the Counter (OTC) without prescription. Hence there is misuse and overuse. Since 1920 when the drug was discovered, much safer alternatives have been launched. Analgin does not appear in the National List of Essential Medicines (NLEM). The approved indication of drug in India is *“severe pain or pain due to tumour and also for bringing down the temperature in refractory cases when other anti-pyretics fail to do so.”* However the product insert of Baralgan-M and Novalgin, the two top selling brands of analgin recommend its use in *“severe or resistant pain and fever”* and the words *“when other anti-pyretics fail to do so”* have been omitted thus leading to over promotion in violation of rules (**Annexure 12**). Analgin crosses the placenta and should not be used during pregnancy. Similarly women who are breast feeding must not use the drug. How many people know this? As per documents submitted by the Ministry, the issue of withdrawing analgin has not been seriously considered.

8.4 **The Committee has noted that there are a very large number of alternative analgesics, antipyretics in the Indian market. With so many countries banning Analgin, not to mention unlawful over-promotion by manufacturers, the CDSCO should be directed to re-examine the rationality of continued marketing of Analgin.**

8.5 **It is to be kept in mind that a drug becomes a candidate for withdrawal not only due to serious side effects but also when safer, more efficacious drugs are launched. Unfortunately, no attention is being paid to this issue. This principle should apply to all cases and all drugs need to be evaluated periodically.**

8.6 In some cases, such as nimesulide, CDSCO officials have argued that *“no adverse reports have been received from India; hence there is no reason to ban.”* Unfortunately the infrastructure and system required to pick up adverse effects in India is lacking. CDSCO has acknowledged that under a World Bank funded programme (23-11-2004 to 30-6-2008) to detect side effects, not a single new adverse drug reaction was reported from anywhere in the country.

8.7 **The documents submitted by the Ministry show that even in large developed countries with well developed drug regulation such as US the adverse reactions are not detected by spontaneous reports from doctors in practice. All major side effects were detected in large scale controlled, focused Post-Marketing Phase IV trials involving thousands of patients such as SCOUT on anti-obesity drug sibutramine (now banned) and the RECORD trial on rosiglitazone (now banned). Therefore to expect that any spontaneous reports from medical profession, either in private practice or even institutions (medical colleges, large hospitals) will pick up hitherto unknown side effects in India is not realistic. There is hardly any alternative but to take immediate cognizance of serious adverse drug reactions reported from countries with well developed and efficient regulatory systems. The health and lives of patients in India cannot be put to risk in the hope of detecting ADRs within the country.**

8.8 **The Committee feels that since the chances of picking up unknown serious adverse effects of drugs being marketed in the country are remote, therefore CDSCO should keep a close watch on regulatory developments that take place in countries with well developed regulatory systems in the West and take appropriate action in the best interest of the patients.**

8.9 On this issue, the responses from the Ministry are vague, not convincing and not to the point. The reply merely states that such dubious drugs are examined in *“consultations with the experts/DTAB.”* The response raises many questions:

- Firstly, at the time of approval of drugs, the matter is not referred to DTAB, then why should DTAB be involved when drugs are to be banned? Secondly, many drugs have been approved by DCGI without consultations with experts; why involve them when banning? There is no answer to these specific questions. It must be made clear that the Committee is not suggesting that DTAB should not be consulted. On the contrary, extensive consultations

should take place not only while banning but also approving the drugs. There should be no double standards.

- There is no standard, uniform, transparent system of referral for expert opinion before a drug is banned. In some cases the opinion of DTAB is obtained such as rimonabant, sibutramine and rosiglitazone; in others it is not obtained but is referred to an Expert Committee appointed by CDSCO such as levonorgesterol, letrozole, nimesulide. In yet other cases such as rofecoxib and valdecoxib, the matter was neither referred to DTAB nor to CDSCO-appointed expert committee.

8.10 In most cases, most of these experts whether appointed by CDSCO or DTAB are from Delhi. The following facts reveal this pattern:

- **Rimonabant was referred to a committee of six experts, all from Delhi.**
- **Levonorgestrel: Four out of five from Delhi.**
- **Letrozole: Four out of five from Delhi.**
- **Sibutramine: All five from Delhi.**
- **Rosiglitazone: All five from Delhi.**

A review of membership shows that one expert sat on 5 of the 6 committees. One wonders whether expertise on drugs is confined to Delhi.

8.11 The Committee strongly recommends that with some 330 teaching medical colleges in the country, there are adequate number of knowledgeable medical experts with experience who can be requested to give their opinion on the safety and efficacy of drugs. The need is to make such consultations very broad based so as to get diverse opinion. The opinions, once received, can be put in public domain inviting comments. Once the experts know that their opinions will be scrutinized by others, including peers, they would be extra cautious and give credible evidence in support of their recommendation.

9. Fixed Dose Combinations (FDCs)

9.1 When two or more drugs, already approved individually, are combined for the first time in an FDC, then under the law the product is deemed to be a New Drug. Such FDCs have to undergo the procedure applicable to New Drugs such as clinical trials etc. to determine safety and efficacy. Once such FDCs receive approval from CDSCO, manufacturers can approach State Drugs Authorities to obtain Manufacturing Licenses.

9.2 Unfortunately some State Drug Authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO. This is in violation of rules though till May 2002, there was some ambiguity on powers of the State Drug Authorities in this respect. However the end result is that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk.

9.3 To remove such unauthorized FDCs from the market, the Central Government can either issue directions under Section 33P to states to withdraw the licences of FDCs granted without prior DCGI approval or the Central Government can itself ban such FDCs under Section 26A.

9.4 The Committee was informed that DCGI has been requesting State Drug Authorities not to issue manufacturing licences to new FDCs and suspend licences of unauthorized FDCs issued in the past. However in exercise of powers under Section 33P specific directions have not been issued. The Ministry failed to provide any coherent reason for lack of action under this Rule. The Ministry informed the Committee that even if Section 33P was invoked, there was no provision to take action against States if directions were not carried out. If considered necessary, the Ministry may examine the possibility of amending the law to ensure that directions under Section 33P are implemented.

9.5 It is also possible to ban FDCs, not authorized by CDSCO by invoking Section 26A which empowers the Central Government to ban any drug to protect public health. The Committee was informed that the Government has not evoked Section 26A either so far. No explanation was offered for not using powers under Section 26A.

9.6 The Committee was informed that the issue regarding grant of Manufacturing Licenses for unapproved FDCs by some State Drug Authorities were first deliberated in 49th DTAB meeting held on 17 February, 2000 i.e. 11 years ago. It is a matter of great concern that even after a lapse of a decade, no serious action has been taken.

9.7 The Committee is of the view that those unauthorized FDCs that pose risk to patients and communities such as a combination of two antibacterials need to

be withdrawn immediately due to danger of developing resistance that affects the entire population.

9.8 The Committee is of the view that Section 26A is adequate to deal with the problem of irrational and/or FDCs not cleared by CDSCO. There is a need to make the process of approving and banning FDCs more transparent and fair. In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC. The Committee strongly recommends that a clear, transparent policy may be framed for approving FDCs based on scientific principles.

10. Drugs Advisory Committees

10.1 The Health Secretary stated that twelve new Drugs Advisory Committees are in the process of being constituted to provide technical inputs and assist CDSCO in examining applications for new drugs to be introduced in the country. These Drugs Advisory Committees would basically be specific subject-oriented and each will have ten experts. These are being constituted so as to further strengthen the reviewing process and they would be permanent in nature. Normally, the Ministry tries to see that eminent people from the institutions such as All India Institute of Medical Sciences or Maulana Azad Medical College are a part of these Committees.

10.2 The Committee feels that though the Ministry is forming DACs, which are given very important powers, there is no transparent procedure for the selection of experts of such Committees. The Committee also recommends that institutions from which experts are chosen should be from different parts of the country.

11. Similar Brand Names

11.1 New drugs are approved by CDSCO under their generic (chemical/salt) names. The brand names are decided by the manufacturers and intimated to State Drug Authorities. Due to lack of coordination between various State Drug Authorities, many identical brands are being used for different medicines by various manufacturers located in different states. For example, Lona is being used for low sodium salt as well as for clonazepam (anti-epilepsy drug); AZ brand is being used

for azithromycin (antibiotic), albendazole (for worms) and alprazolam (for anxiety). Needless to say this is a highly dangerous situation where wrong medicine can be sold and consumed leading to serious injury. CDSCO has expressed its inability to resolve the issue due to lack of rules and powers.

11.2 The Committee strongly recommends that all such cases should be thoroughly reviewed in close coordination with State Drug Authorities. Specific procedures may be framed for approval of brand names. The procedure adopted by the Registrar of Newspapers to avoid duplication may be worth emulating. As a beginning, a data bank of all branded pharmaceutical products along with their ingredients should be uploaded on the CDSCO website and regularly updated.

12. Post-marketing Surveillance

12.1 Once New Drugs are approved, rules require that manufacturers submit post-marketing Periodic Safety Update Reports (PSURs) listing side effects, fatalities, injuries etc. in Indian patients once every six months in the first two years and then annually in the following two years.

12.2 In order to scrutinize the compliance of this rule, the Ministry was asked to furnish PSURs in respect of 42 randomly selected new drugs. Since files in respect of three drugs were reportedly missing, PSURs should have been supplied for the balance 39 drugs. The Committee is, however, constrained to note that PSURs in respect of only 8 drugs were submitted by the Ministry. The Committee was informed that 14 drugs though approved were not being marketed or were launched lately and hence PSURs would be expected later. There was no explanation for not submitting PSURs in respect of rest of 17 drugs.

12.3 Out of 14 drugs that were reported to be either not yet launched or lately launched, the Committee discovered that, at least, two products (FDC of glucosamine with ibuprofen; and moxonidine) were indeed in the market for some time and concerned manufacturers should have submitted PSURs. But the Committee has not been given any explanation for non-submission of PSURs for these two drugs.

12.4 The Committee observed that even, in those cases where the PSURs were submitted, the frequency and/or format was not as per rules. In the case of two drugs of MNCs (dronedarone of Sanofi Aventis and pemetrexid of Eli Lilly), the

PSURs were neither India specific nor in the approved format as required by law. Some companies submitted PSURs for the products being marketed in the country but very few PSURs were India-specific.

12.5 The Committee is of the firm view that there is a poor follow-up of side effects in Indian patients both by doctors and manufacturers. The objective of PSURs is to collect information about adverse effects on patients in India which would help to determine ethnic differences, if any and result in dosage adjustment, revision of precautions and warnings, if necessary. The Committee takes strong exception to such rampant violation of the mandatory requirements.

12.6 The Committee strongly recommends that the Ministry should direct CDSCO to send a stern warning to all manufacturers of new drugs to comply with mandatory rules on PSURs or face suspension of Marketing Approval. PSURs should be submitted in CDSCO-approved format which would help track adverse effects discovered in Indian ethnic groups.

13. Pharmacovigilance

13.1 The Committee was informed that the Ministry has recently launched 'Pharmacovigilance Scheme' that will enable CDSCO to collect adverse drugs reactions data in a systematic manner. This data will be used while taking decisions on banning/placing of restrictions on drugs along with data from abroad. The Health Secretary further clarified that medical colleges are enrolled in pharmacovigilance in phases as monitoring centres. Forty-three colleges were already enrolled and they hope to go up to 75 by adding more. But, ultimately, the aim was to include all the medical colleges in the country under this programme so that the spread of pharmacovigilance programme is across the country.

13.2 Determination of side effects of marketed medicines is an extremely complicated exercise that requires infrastructure, appropriate result-oriented methodology and expertise. CDSCO has admitted that in the past in the World Bank funded project, not even one additional hitherto unknown serious side effect was identified worth reporting to the global WHO monitoring centre in Sweden. In the

period 2006 to 2010, other Drugs Regulatory Authorities discovered the following number of serious ADRs:

USFDA (United States)	223
Health Canada	123
MHRA (Britain)	85
Medsafe (New Zealand)	62
EMA (European Community)	59
TGA (Australia)	45

13.3 The Committee feels that the conventional system of locating side effects through spontaneous reporting by doctors to either drug companies or drug regulators has been found to be unsatisfactory. The most effective system is by controlled post-marketing Phase IV studies on a very large number of patients. In the past decade, all the major adverse effects that led to banning of drugs were identified in large scale Phase IV trials. The Ministry may wish to consider the possibility of using this format in the country.

14. Updation of Information on Marketed Drugs

14.1 Based on inputs from drug regulatory authorities in different countries rapid changes are taking place in the dosage, safety, efficacy and precautions of currently approved drugs leading to alterations in authorized monographs (prescribing information and safety guidelines). For example it was not earlier known that the drug modafinil can cause serious skin reactions, that concurrent use of two anti-hypertensive agents, telmisartan with ramipril, is risky etc. To protect patients, it is vital that approved prescribing information is updated and amended as soon as new information is received. Accordingly, the Committee asked the Ministry to give details of changes in the prescribing information on drugs sold in India in the year 2009 and 2010. In response the Ministry submitted a list of just 14 products, that too only from MNCs. During the same period WHO in its publicly available Bulletin gave information on changes in 274 medicines while USFDA and British MHRA ordered changes in over 500 drugs.

14.2 One of the conditions while approving drugs is obligation on the part of manufacturers to intimate all changes in efficacy, safety, dosage, side effects etc. that may take place globally. Apparently manufacturers are not submitting such vital

information to the CDSCO in violation of rules and continue to use outdated information in their promotion, label, package insert etc. Naturally patients are suffering. CDSCO also failed in its statutory duty of enforcing laws and penalizing those who did not comply with rules on updation of information.

14.3 The Committee feels that unless information on marketed drugs is continuously updated, there is risk of irrational or inappropriate use of medicines putting patients at risk. The Committee, therefore, recommends that immediate steps need to be taken to address this issue. The CDSCO should be directed to continuously update monographs based on information from regulatory authorities the world over.

15. Spurious/Sub-standard Drugs

15.1 The Committee was apprised that the propaganda on alleged availability of spurious drugs is motivated and manipulated by foreign drug manufacturers with a view to damage the reputation of Indian domestic manufacturers, who have successfully competed with MNCs in both domestic sales and export at much lower prices. The MNCs are deliberately confusing the issue by clubbing and interchanging 'spurious' with 'counterfeit' drugs. The Indian definition of counterfeit refers to the unauthorized use of a registered brand name, even when the product is of acceptable quality. The Western definition is far wider and includes the so-called 'generic' medicines manufactured by anyone other than patent holders without innovators permission, even when there is no valid patent in India. If the medicines are of high quality and legally produced in India, they are still dubbed as 'counterfeits' by innovators in the West. According to a study by the CDSCO, the prevalence of spurious drugs in India is less than 0.5 per cent as against the allegations by MNCs of 25-30 percent.

15.2 Taking advantage of the confusion created by MNCs over fake and counterfeits, the so-called anti-counterfeit solution providers that sell barcode and other technologies are propagating and lobbying for the use of such expensive, impractical methods by making them legally compulsory. Use of barcodes will increase the cost of drugs without any benefit to consumers.

15.3 The Committee observed that, unfortunately, the problem with sub-standard, classified as 'Not of Standard Quality' drugs is more serious. An analysis of the data generated by State and Central drug testing laboratories shows the prevalence to be in the region of 7-8 per cent over the past decade.

15.4 A drug can be categorized 'Not of Standard Quality' for a variety of both major and minor technical reasons such as not stating the name of the pharmacopoeia correctly, problem with quality of bonding agent, colouring agent, dissolution time, etc. However, there are other more serious cases, where the active ingredient is significantly less in quantity that can harm patients. Therefore, this problem needs to be addressed with all the seriousness that it deserves both by more rigorous checks in procuring bulk drugs (particularly from developing countries with not so stringent quality checks and export controls) and by in-house quality control by manufacturers or solving the problem in transportation and/or storage at distribution/retail levels.

15.5 By the time a sample is tested, a large number of packs get sold out with undeterminable injury to patients. There is no effective method of recalling unsold stocks lying in the distribution network. This cannot be allowed to go on.

15.6 The Committee feels that there should be severe punishment for manufacturing and for allowing sub-standard drugs to enter the distribution chain. Products with severe deficiencies should be penalized the same way as producers of spurious drugs by amending rules. There is also a case to incorporate penal provisions for manufacturing misbranded and adulterated drugs.

15.7 It is known that retail chemists also stock and sell items other than drugs including chocolates, cold drinks etc. During summer these items are stored in the refrigerator while due to paucity of space temperature-sensitive medicines may be lying outside. When samples are picked up, tested and found to be sub-standard, the State Drug Authorities blame and prosecute manufacturers. Therefore the Committee recommends that specifically in the case of temperature sensitive products such as insulins, due consideration should be given to the reference samples of the same batch preserved by the manufacturers.

15.8 A large number of finished ready-to-use drugs, in excess of 1,000 have been approved by CDSCO to be imported not only by pharmaceutical companies but

traders as well. Most traders import and sell the drugs directly to patients on receiving tips from prescribers. The Ministry informed the Committee that random samples of such finished formulations are collected at the port of entry and tested by approved laboratories. However there is no mechanism in place to test such formulations once they leave the port of entry because they are not sold at retail chemists. Drugs inspectors collect samples from either the premises of manufacturers or more commonly from retailers. Most of such imported drugs are highly temperature-sensitive and may lose their potency if not stored properly. There is no procedure to test drugs being sold outside the retail chain. Besides being exorbitantly expensive, there is always the possibility of spurious/duplicates entering the supply chain. For example just one ampoule of anti-cancer drug, Herceptin, is priced at over Rs. 1.20 lacs.

15.9 The Committee is extremely anxious on both counts: such hugely costly imported drugs losing their potency before use and the possibility of fakes entering the chain. It is strange that multinational drug companies that have well staffed marketing offices in India, instead of importing drugs from their overseas affiliates and selling them are using traders to handle this activity. Apart from risk to patients, there is leakage of revenue to income tax. While the promotional expenses on imported formulations are being paid by the Indian branch of MNCs thus reducing income tax liability, there is no corresponding income since traders are paying directly to overseas offices of MNCs. The Committee would like the Ministry to ensure that in cases where MNCs have offices in India, traders are not permitted to import formulations of such companies. The Committee would like to be kept informed of the steps taken on this issue.

15.10 The Ministry has recently approved a programme for CDSCO for conducting inspections of drug manufacturing sites located abroad to ensure that only quality drugs, including bulk drugs registered and compliant with the regulatory norms in the countries of origin are imported into our country.

15.11 The Committee recommends that once a batch of a drug is found to be sub-standard and reported to CDSCO, it should issue a press release forthwith and even insert paid advertisements in the newspapers apart from uploading the information on the CDSCO website. Retail chemists should be advised to stop

selling unsold stocks and return the same to local Drugs Inspectors as per rules. The Committee understands that at least two State Drug Authorities, that of Maharashtra and Kerala, have taken the initiative to upload information on spurious and sub-standard drugs on their websites on a monthly basis. These are welcome measures worth emulating by other states and the Centre.

16. Advertising of Prescription Drugs in the Lay Media

16.1 It has come to the notice of the Committee that some manufacturers advertise prescription drugs (Schedule H) in the lay press. Based on incomplete information, patients tend to self-medicate more so because such medicines are generally available without prescription. Such practices can adversely impact not only the health of individuals but even communities and countries. For example misuse of antibiotics can lead to bacterial resistance with serious consequences for public health. Recent cases of lay press advertisements are those of:

- Anti-depressant Deanxit (Lundbeck) (**Annexure 13**)
- Anti-epileptic agents Desval ER (Ranbaxy), Lametec DT (Cipla), C-Toin (USV)
- Cholesterol lowering Coltro (USV).

16.2 **The Committee would like the Ministry to take appropriate action against the companies that have advertised the above Schedule H drugs in the lay press. The provisions in the Drugs and Magic Remedies Act are not stringent enough with the result that manufacturers violate them at will. It also recommends that apart from giving sharper teeth to the Drugs and Magic Remedies Act, a provision should also be incorporated in the Drugs and Cosmetics Rules to ban such practices and penalize offenders. The Committee would like to be informed of the action taken to implement these recommendations.**

17. Consumer Information

17.1 Explaining about labels and package inserts, the Committee was informed that although label was mandatory for manufacturers, to provide package inserts with each pack of drugs were not mandatory. It was also stated that labels are meant for consumers while package inserts are meant for doctors. Even when they are provided by manufacturers in the outer carton in insufficient numbers (for example just one insert in a box of 10 strips), they are in technical language and

strangely state that they are “for use of medical practitioners”, even though they are supplied to consumers.

17.2 The Committee was informed that there is no mandatory provision of providing information to the consumers of drugs in the form of Product Information Leaflet (mandatory in western countries) in simple language. The Committee feels that in our country, overworked doctors do not have the time to explain the use, side effects, drug interactions and other precautions to be taken while taking prescribed drugs to each and every patient. According to World Medicines Situation, 2011 of the WHO, doctors in developing countries spend less than 60 seconds in prescribing and explaining the therapy to patients. Thus, patients are at risk because of lack of information on proper use of drugs, expected side effects etc. The label on the product, mostly written in very small print, does not carry information useful to patients.

17.3 The Committee is of the firm opinion that accurate information on drugs for patients is absolutely essential to prevent inappropriate use more particularly in children, elderly, during pregnancy and lactation. The Committee recommends that the matter may be looked into to ensure that consumers have the required information to use medicines safely. Given the widespread internet connectivity, it is advisable to devise a system where patients can get unbiased information on drugs at the click of the mouse in any language.

18. Clinical Trials on New Drugs

18.1 A very larger number of clinical trials are being conducted in India after liberalization of relevant Rules (Schedule Y) in January, 2005. The Committee was informed that a total of 2,282 trials have been approved from the year 2005 up to September, 2010. The Committee also observed that there has been extensive media coverage, both in India and abroad such as BBC, US NBC, French TV, Al Jazeera etc. with serious, documented cases of poor, illiterate citizens including children of India being used as 'guinea pigs' by MNC drug manufacturers. As per the Ministry's status note, a total of 1,514 subjects have died in the years 2008 to August 2010 during clinical trials. In some isolated cases, in response to media reports, CDSCO investigated the trials and found irregularities.

18.2 Due to the sensitive nature of clinical trials in which foreign companies are involved in a big way and a wide spectrum of ethical issues and legal angles, different aspects of Clinical trials need a thorough and in-depth review. This Committee has, accordingly, taken it up as a subject for detailed examination separately under the heading 'Clinical Trials of Drugs'.

2. MANDATE AND STRUCTURE OF CDSCO

The Committee is of the firm opinion that most of the ills besetting the system of drugs regulation in India are mainly due to the skewed priorities and perceptions of CDSCO. For decades together it has been according primacy to the propagation and facilitation of the drugs industry, due to which, unfortunately, the interest of the biggest stakeholder i.e. the consumer has never been ensured. Taking strong exception to this continued neglect of the poor and hapless patient, the Committee recommends that the Mission Statement of CDSCO be formulated forthwith to convey in very unambiguous terms that the organization is solely meant for public health. (Para 2.2)

The Committee notes with serious concern that CDSCO is substantially under-staffed. Of the 327 sanctioned posts, only 124 are occupied. At this rate, what would be the fate of 1,045 additional posts that have been proposed is a moot point. If the manpower requirement of the CDSCO does not correspond with their volume of work, naturally, such shortage of staff strains the ability of the CDSCO to discharge its assigned functions efficiently. This shortcoming needs to be addressed quickly. Consideration can also be given to employ medically qualified persons as Consultants/Advisers (on the pattern of Planning Commission) at suitable rank. (Para 2.19)

The Committee also gathers that the average time taken for the completion of recruitment process is approximately 12 to 15 months. The Committee, therefore, recommends that to overcome the staff shortage, the Ministry should engage professionally qualified persons on short-term contract or on deputation basis until the vacancies are filled up. Due to the very sensitive nature of regulatory work, great care will need to be taken to ensure that persons employed for short periods did not and will not have Conflict of Interest for a specified period. (Para 2.20)

At the same time, the optimal utilization of the current staff in the best interest of public is the responsibility of those who run the CDSCO. In a resource-constrained country like India, it is extremely difficult to meet the demands,

however, genuine, of all the State entities in full. Hence, prioritization is the key. For example, work relating to an application for Marketing Approval of a New Drug that will be used by millions and thus have an impact on the well being of public at large in India for years to come, is far more important and urgent than giving permission to a foreign company to conduct clinical trials on an untested new patented, monopoly drug. (Para 2.21)

The Committee also observes that the strengthening of drugs regulatory mechanisms cannot be achieved by manpower augmentation alone. A host of issues involving capacity-building of CDSCO like upgradation of existing offices, setting up of new offices, creation of new central drugs testing laboratories and equipping them with the state-of-the-art technology to enable them to carry out sophisticated analysis of drugs, upgradation of the existing 6 Central Drugs Testing Laboratories, skill development of the regulatory officials, implementation of an effective result-oriented pharmacovigilance programme drawing on global experience, increased transparency in decision-making of CDSCO etc. will have to be addressed before the desired objectives are realized. (Para 2.22)

In the absence of any reasons for unwillingness on the part of medically qualified persons to join CDSCO, the Committee is of the opinion that emoluments and perquisites may not be the main or only reason. It is noticed that minimum prescribed academic qualifications for the post of DCGI is barely B.Pharm. On the other hand for Deputy Drugs Controller (DDC), the prescribed minimum qualification is post-graduation for medically qualified persons. The stumbling block is the requirement that DCGI should have experience in the "manufacture or testing of drugs or enforcement of the provisions of the Drugs and Cosmetic Act for a minimum period of five years." This requirement virtually excludes even highly qualified medical doctors from occupying the post of DCGI. Moreover the rule stipulates that doctors with post-graduation should be either in pharmacology or microbiology only, thus excluding post-graduates, even doctorates (like DM) in a clinical subject. Besides, highly qualified medical doctors may be reluctant to work under and report to a higher officer with lesser qualifications in a technology driven regulatory authority set-up. Unless these

concerns are addressed, it would be difficult to get the desperately required medically qualified professionals on the rolls of CDSCO. (Para 2.23)

3. QUALIFICATION AND POWERS of DCGI

The Committee fails to understand as to how a graduate in pharmacy or pharmaceutical chemistry (B.Pharm) is being equated with a medical graduate with MD in Pharmacology or Microbiology. Apart from the obvious anomaly, with rapid progress in pharmaceutical and biopharmaceutical fields, there is urgent need to revise the qualifications and experience as minimum eligibility criteria for appointment as DCGI. The Committee is of the view that it is not very rational to give powers to a graduate in pharmacy, who does not have any clinical or research experience to decide the kinds of drugs that can be prescribed by super specialists in clinical medicine such as those holding DM and PhD qualifications and vast experience in the practice of medicine and even research. (Para 3.6)

On a larger plane, the Committee is disillusioned with the qualifications provided in the age old Rules for the head of a crucial authority like CDSCO. The extant Indian system is nowhere in so far as sheer competence and professional qualifications are concerned when compared with countries like USA and UK. There is, therefore, an urgent need to review the qualifications, procedure of selection and appointment, tenure, emoluments, allowances and powers, both administrative and financial of the DCGI. While doing so, the Government may not only rely on the Mashelkar Committee Report which recommended augmented financial powers to DCGI but also take cue from similar mechanisms functioning in some of the developed countries like USA, UK, Canada, etc in order to ensure that only the best professional occupies this onerous responsibility. The Committee should be kept informed of the steps taken to address this issue. (Para 3.7)

In the considered opinion of the Committee, there can never be a more opportune time than now, to usher in these changes recommended by it. The post of DCGI is vacant as of now, with an official holding temporary charge. They, therefore, desire that the government should take immediate measures in terms of

their instant recommendations to ensure that CDSCO is headed by an eminent and professionally qualified person. (Para 3.8)

4. ROLE OF THE STATE DRUG REGULATORY AUTHORITIES

From an analysis of the above facts, the Committee concludes that shortcomings witnessed in respect of coordination with and between the States as also in implementation of applicable legislations in the States are primarily an offshoot of inadequacies in manpower and infrastructure in the States. Strengthening the regulatory mechanism in the States will remain a far cry unless these infirmities are taken care of.

(Para 4.5)

Given the lack of adequate resources in the States it would be unrealistic to expect them to improve the infrastructure and increase manpower without Central Assistance for strengthening drug control system. The Committee, therefore, recommends that the Ministry of Health and Family Welfare should work out a fully centrally sponsored scheme for the purpose so that the State Drug Regulatory Authorities do not continue to suffer from lack of infrastructure and manpower anymore. The Committee desires to be kept apprised of the initiatives taken by the Ministry in this regard. (Para 4.6)

It is a matter of grave concern that there are serious shortcomings in Centre-State coordination in the implementation of Drugs & Cosmetics Act and Rules. This, the Committee notes, is despite the Ministry's own admission that Section 33P of the Drugs and Cosmetics Act contains a provision that enables the Central Government to give such directions to any State Government as may appear to it to be necessary for implementation of any of the provisions of the Drugs and Cosmetics Act and Rules made thereunder. The Committee understands that these provisions are meant to be used sparingly. However, there have been several situations which warrant intervention through Rule 33 P. Therefore the committee hopes that in future the Ministry would not be found wanting in considering the option of using Section 33P to ensure that provisions of central drug acts are implemented uniformly in all states. (Para 4.7)

As regards lack of databank and accurate information, the Committee would like to observe that given the information technology resources currently available, developing an effective system of coordination amongst State Drug Authorities for providing quality and accurate data could have been accomplished long back had the Ministry taken any initiative towards encouraging the States to establish a system of harmonized and inter-connected databanks. Evidently, no serious efforts seem to have been made in this regard. The Committee, however, expects that the Ministry would, at least now, play a more pro-active role in encouraging the States to employ modern information technology in the implementation of tasks assigned to them. At the same time a centralized databank (e.g. licenses issued, cancelled, list of sub-standard drugs, prosecutions etc.) may be created to which all the State Drug Authorities should be linked.

(Para 4.8)

5. CAPACITY-BUILDING OF CENTRAL AND STATE DRUG TESTING LABORATORIES

The Committee agrees that the capacity-building of the Central Drugs Testing Laboratories is the need of the hour. In this era of newer innovations coming up at rapid pace, equipping the Drug Testing Laboratories with the high-end sophisticated equipments is very essential. However, the Committee is aware that monitoring the quality of drugs is primarily the responsibility of the State Drugs Authorities, supplemented by CDSCO, which play a major role in collection of samples and testing them. Without manpower augmentation and upgradation of State Drugs Testing Laboratories, the objective of ensuring availability of quality drugs to the public cannot be realized. The Committee, therefore, recommends strengthening of both Central and State Drug Testing Laboratories.

(Para 5.11)

6. PROVISION OF REQUISITE INFRASTRUCTURE AT AIRPORT AND SEAPORT OFFICES

The Committee agrees with the above suggestion and recommends that the Ministry of Health and Family Welfare should take initiative towards addressing the shortcomings forthwith in coordination with the Ministry of Civil Aviation at all seaports/airports handling import and exports of pharmaceutical products. The

Committee will like to be informed of steps taken to address this problem.

(Para 6.2)

7. NEW DRUGS APPROVAL

The Committee is of the view that due to untraceable files on three drugs, it is not possible to determine if all conditions of approval (indications, dosage, safety precautions) are being followed or not. Moreover the product monographs cannot be updated in the light of recent developments and regulatory changes overseas. Therefore all the missing files should be re-constructed, reviewed and monographs updated at the earliest.

(Para 7.13)

.....This matter needs to be reviewed to ensure safety of patients, fair play, transparency and accountability.

(Para 7.14)

Unless there is some legal hitch, the Committee is of the view that there is no justification in withholding opinions of experts on matters that affect the safety of patients from public. Consideration should be given to upload all opinions on CDSCO website.

(Para 7.15)

According to information provided by the Ministry, a total of 31 new drugs were approved in the period January 2008 to October 2010 without conducting clinical trials on Indian patients. The figure is understated because two drugs (ademetonine and FDC of pregabalin with other ingredients) were somehow not included in the list. Thus there is no scientific evidence to show that these 33 drugs are really effective and safe in Indian patients.

(Para 7.16)

It is obvious that DCGI clears sites of pre-approval trials without application of mind to ensure that major ethnic groups are enrolled in trials to have any meaningful data. Thus such trials do not produce any useful data and merely serve to complete the formality of documentation.

(Para 7.27)

The Committee recommends that while approving Phase III clinical trials, the DCGI should ensure that subject to availability of facilities, such trials are spread across the country so as to cover patients from major ethnic backgrounds and ensure a truly representative sample. Besides, trials should be conducted in well equipped medical colleges and large hospitals with round the clock emergency services to handle unexpected serious side effects and with expertise

in research and not in private clinics given the presence of well equipped medical colleges and hospitals in most parts of the country in present times. (Para 7.28)

The Committee is of the view that taking into account the size of our population and the enormous diversity of ethnic groups there is an urgent need to increase the minimum number of subjects that ought to be included in Phase III pre-approval clinical trials to determine safety and efficacy of New Drugs before marketing permission is granted. In most western countries the required numbers run into thousands. However since the major objective in India is to determine the applicability or otherwise of the data generated overseas to Indian population, the requirement should be re-assessed and revised as per principles of medical statistics so that major ethnic groups are covered. A corresponding increase in the number of sites so as to ensure a truly representative sample spread should also be laid down in black and white. Furthermore, it should be ensured that sites selected for clinical trials are able to enroll diverse ethnic groups. For domestically discovered drugs, the number of subjects should be revised as well. This can be easily achieved by changes in the Good Clinical Practice (GCP) guidelines.

(Para 7.29)

A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data. Such opinions are of extremely limited value and merely a formality. Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures..... Is the Committee mistaken in coming to the conclusion that all these letters were collected by interested party from New Delhi, Mumbai, Chandigarh and Secunderabad and handed over to office of the DCGI on the same day? If so, it is obvious that the interested party was in the loop in the entire process of consultation with experts. (Annexure 6).....It is inconceivable that a letter dated 17-6-2005 from New Delhi will be delivered to the office of DCGI also in New Delhi after more than two months. The conclusion, as in aforementioned cases, is obvious. (Annexure 8)

(Para 7.31)

If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more outrageous than clinical trial approval given to the Fixed Dose Combination of aceclofenac with drotaverine which is not permitted in any developed country of North America, Europe or Australasia. In this case, vide his letter number 12-298/06-DC dated 12-2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not only to select experts but get their opinions and deliver them to the office of DCGI! No wonder that many experts gave letters of recommendation in identical language apparently drafted by the interested drug manufacturer. (Para 7.32)

In the above case, the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug. (Para 7.33)

Such expert opinions in identical language and/or submitted on the same day raise one question: Are the experts really selected by the staff of CDSCO as mentioned in written submission by the Ministry? If so how can they, situated thousands of miles away from each other, draft identically worded letters of recommendation? Is it not reasonable to conclude the names of experts to be consulted are actually suggested by the relevant drug manufacturers? It has been admitted that CDSCO does not have a data bank on experts, that there are no guidelines on how experts should be identified and approached for opinion. (Para 7.34)

The Committee is of the view that many actions by experts listed above are clearly unethical and may be in violation of the Code of Ethics of the Medical Council of India applicable to doctors. Hence the matter should be referred to MCI for necessary follow up and action. In addition, in the case of government-employed doctors, the matter must also be taken up with medical colleges/hospital authorities for suitable action. (Para 7.35)

There is sufficient evidence on record to conclude that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts. (Para 7.36)

On a more fundamental issue the Committee has come to the conclusion that when it comes to approving new drugs, too much is left to the absolute discretion of the CDSCO officials. There are no well laid down guidelines for determining whether consultation with experts is required. Thus the decision to seek or not to seek expert opinion on new drugs lies exclusively with the non-medical functionaries of CDSCO leaving the doors wide open to the risk of irrational and incorrect decisions with potential to harm public health apart from the possibility of abuse of arbitrary discretionary powers. (Para 7.37)

The Committee, therefore, strongly recommends that there should be non-discretionary, well laid down, written guidelines on the selection process of outside experts with emphasis on expertise including published research, in the specific therapeutic area or drug or class of drugs. Currently, the experts are arbitrarily chosen mainly based on their hierarchical position which does not necessarily correspond to the area or level of expertise. All experts must be made to file the Conflict of Interest declaration outlining all past and present pecuniary relationships with entities that may benefit from the recommendations given by such experts. The consulted experts should be requested to give hard evidence in support of their recommendations. (Para 7.38)

The Committee is of the view that responsibility needs to be fixed for unlawfully approving Buclizine, a drug of hardly any consequence to public health in India, more so since it is being administered to babies/children. At the same time the approval granted should be reviewed in the light of latest scientific evidence, regulatory status in developed countries, particularly in Belgium, the country of its origin. (Para 7.41)

.....DCGI is expected to take action against those CDSCO functionaries who colluded with private interests and got the drug approved in violation of laws. The drug has since been banned by the Ministry for use in female infertility. (Para 7.42)

The Committee takes special note of this case of gross violation of the laws of the land by the CDSCO. First, in approving the drug for use in case of female infertility and thereafter, in exhibiting overt resistance in taking timely corrective steps despite very strong reasons favouring immediate suspension of use of

letrozole for the said indication. Belatedly, the drug has been banned for use in female infertility. (Para 7.43)

The Committee is of the opinion that there must be some very good reasons for Danish Medicine Agency (Denmark) not to approve a domestically developed drug where an anti-depressant drug would perhaps be in greater demand as compared to India. Curiously, Deanxit is allowed to be produced and exported but not allowed to be used in Denmark. (Para 7.45)

The Committee feels that the DCGI should have gone into the reasons for not marketing the drug in major developed countries such as United States, Britain, Ireland, Canada, Japan, Australia just to mention a few. United States alone accounts for half of the global drug market. It is strange that the manufacturer is concentrating on tiny markets in unregulated or poorly regulated developing countries like Aruba, Bangladesh, Cyprus, Jordan, Kenya, Myanmar, Pakistan, and Trinidad instead of countries with far more patients and profits. Many of these developing countries are handicapped due to lack of competent drug regulatory authorities. Instead of examining and reversing regulatory lapses, DCGI has referred the matter to an Expert Committee to look at the isolated and restricted issue of "safety and efficacy" instead of unlawful approval in the first place. (Para 7.46)

The Committee recommends that in view of the unlawful approval granted to Deanxit, the matter should be re-visited and re-examined keeping in mind the regulatory status in well developed countries like Denmark, the country of origin; the United States, Britain, Canada, European Union and Japan etc. It is important to keep in mind that in Europe, there are two types of marketing approvals: Community-wide (cleared by European Medicine Agency) and individual regulators of member nations. EMEA is known to clear drugs after great deal of scrutiny while the competence and expertise of drug regulatory authorities of individual nations is not uniform and varies greatly from country to country. (Para 7.47)

The Committee recommends an enquiry into the said letter. The responsibility should be fixed and appropriate action taken against the guilty. The Committee should be kept informed on this case. (Para 7.49)

The Committee takes special notice of this case of persistent insolence on the part of CDSCO and hopes that never again shall the DCGI approve drugs in violation of laws, that too for use in neonates and young children.

(Para 7.51)

The Committee expresses its deep concern, extreme displeasure and disappointment at the state of affairs as outlined above. The Ministry should ensure that the staff at CDSCO does not indulge in irregularities in approval process of new drugs that can potentially have adverse effect on the lives of people. It is difficult to believe that these irregularities on the part of CDSCO were merely due to oversight or unintentional. Hence all the cases listed above and cases similar to these should be investigated and responsibility fixed and action taken against erring officials whether currently in service or retired. (Para 7.52)

8. DRUGS WITHDRAWN/DISCARDED/BANNED ABROAD.

The Committee has noted that there are a very large number of alternative analgesics, antipyretics in the Indian market. With so many countries banning Analgin, not to mention unlawful over-promotion by manufacturers, the CDSCO should be directed to re-examine the rationality of continued marketing of Analgin. (Para 8.4)

It is to be kept in mind that a drug becomes a candidate for withdrawal not only due to serious side effects but also when safer, more efficacious drugs are launched. Unfortunately, no attention is being paid to this issue. This principle should apply to all cases and all drugs need to be evaluated periodically.

(Para 8.5)

The documents submitted by the Ministry show that even in large developed countries with well developed drug regulation such as US the adverse reactions are not detected by spontaneous reports from doctors in practice. All major side effects were detected in large scale controlled, focused Post-Marketing Phase IV trials involving thousands of patients such as SCOUT on anti-obesity drug sibutramine (now banned) and the RECORD trial on rosiglitazone (now banned). Therefore to expect that any spontaneous reports from medical profession, either in private practice or even institutions (medical colleges, large

hospitals) will pick up hitherto unknown side effects in India is not realistic. There is hardly any alternative but to take immediate cognizance of serious adverse drug reactions reported from countries with well developed and efficient regulatory systems. The health and lives of patients in India cannot be put to risk in the hope of detecting ADRs within the country. (Para 8.7)

The Committee feels that since the chances of picking up unknown serious adverse effects of drugs being marketed in the country are remote, therefore CDSCO should keep a close watch on regulatory developments that take place in countries with well developed regulatory systems in the West and take appropriate action in the best interest of the patients. (Para 8.8)

In most cases, most of these experts whether appointed by CDSCO or DTAB are from Delhi. The following facts reveal this pattern:

- Rimonabant was referred to a committee of six experts, all from Delhi.
- Levonorgestrel: Four out of five from Delhi.
- Letrozole: Four out of five from Delhi.
- Sibutramine: All five from Delhi.
- Rosiglitazone: All five from Delhi.
-

A review of membership shows that one expert sat on 5 of the 6 committees. One wonders whether expertise on drugs is confined to Delhi. (Para 8.10)

The Committee strongly recommends that with some 330 teaching medical colleges in the country, there are adequate number of knowledgeable medical experts with experience who can be requested to give their opinion on the safety and efficacy of drugs. The need is to make such consultations very broad based so as to get diverse opinion. The opinions, once received, can be put in public domain inviting comments. Once the experts know that their opinions will be scrutinized by others, including peers, they would be extra cautious and give credible evidence in support of their recommendation. (Para 8.11)

9. FIXED DOSE COMBINATIONS (FDCs)

Unfortunately some State Drug Authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO. This is in violation of rules though till May 2002, there was some ambiguity on powers of the State Drug Authorities in this respect. However the end result is

that many FDCs in the market have not been tested for efficacy and safety. This can put patients at risk. (Para 9.2)

To remove such unauthorized FDCs from the market, the Central Government can either issue directions under Section 33P to states to withdraw the licences of FDCs granted without prior DCGI approval or the Central Government can itself ban such FDCs under Section 26A. (Para 9.3)

The Committee was informed that DCGI has been requesting State Drug Authorities not to issue manufacturing licences to new FDCs and suspend licences of unauthorized FDCs issued in the past. However in exercise of powers under Section 33P specific directions have not been issued. The Ministry failed to provide any coherent reason for lack of action under this Rule. The Ministry informed the Committee that even if Section 33P was invoked, there was no provision to take action against States if directions were not carried out. If considered necessary, the Ministry may examine the possibility of amending the law to ensure that directions under Section 33P are implemented. (Para 9.4)

It is also possible to ban FDCs, not authorized by CDSCO by invoking Section 26A which empowers the Central Government to ban any drug to protect public health. The Committee was informed that the Government has not evoked Section 26A either so far. No explanation was offered for not using powers under Section 26A. (Para 9.5)

The Committee was informed that the issue regarding grant of Manufacturing Licenses for unapproved FDCs by some State Drug Authorities were first deliberated in 49th DTAB meeting held on 17 February, 2000 i.e. 11 years ago. It is a matter of great concern that even after a lapse of a decade, no serious action has been taken. (Para 9.6)

The Committee is of the view that those unauthorized FDCs that pose risk to patients and communities such as a combination of two antibacterials need to be withdrawn immediately due to danger of developing resistance that affects the entire population. (Para 9.7)

The Committee is of the view that Section 26A is adequate to deal with the problem of irrational and/or FDCs not cleared by CDSCO. There is a need to make

the process of approving and banning FDCs more transparent and fair. In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC. The Committee strongly recommends that a clear, transparent policy may be framed for approving FDCs based on scientific principles. (Para 9.8)

10. DRUGS ADVISORY COMMITTEES

The Committee feels that though the Ministry is forming DACs, which are given very important powers, there is no transparent procedure for the selection of experts of such Committees. The Committee also recommends that institutions from which experts are chosen should be from different parts of the country. (Para 10.2)

11. SIMILAR BRAND NAMES

The Committee strongly recommends that all such cases should be thoroughly reviewed in close coordination with State Drug Authorities. Specific procedures may be framed for approval of brand names. The procedure adopted by the Registrar of Newspapers to avoid duplication may be worth emulating. As a beginning, a data bank of all branded pharmaceutical products along with their ingredients should be uploaded on the CDSCO website and regularly updated. (Para 11.2)

12. POST-MARKETING SURVEILLANCE

In order to scrutinize the compliance of this rule, the Ministry was asked to furnish PSURs in respect of 42 randomly selected new drugs. Since files in respect of three drugs were reportedly missing, PSURs should have been supplied for the balance 39 drugs. The Committee is, however, constrained to note that PSURs in respect of only 8 drugs were submitted by the Ministry. The Committee was informed that 14 drugs though approved were not being marketed or were launched lately and hence PSURs would be expected later. There was no explanation for not submitting PSURs in respect of rest of 17 drugs. (Para 12.2)

Out of 14 drugs that were reported to be either not yet launched or lately launched, the Committee discovered that, at least, two products (FDC of glucosamine with ibuprofen; and moxonidine) were indeed in the market for some time and concerned manufacturers should have submitted PSURs. But the Committee has not been given any explanation for non-submission of PSURs for these two drugs. (Para 12.3)

The Committee observed that even, in those cases where the PSURs were submitted, the frequency and/or format was not as per rules. In the case of two drugs of MNCs (dronedarone of Sanofi Aventis and pemetrexid of Eli Lilly), the PSURs were neither India specific nor in the approved format as required by law. Some companies submitted PSURs for the products being marketed in the country but very few PSURs were India-specific. (Para 12.4)

The Committee is of the firm view that there is a poor follow-up of side effects in Indian patients both by doctors and manufacturers. The objective of PSURs is to collect information about adverse effects on patients in India which would help to determine ethnic differences, if any and result in dosage adjustment, revision of precautions and warnings, if necessary. The Committee takes strong exception to such rampant violation of the mandatory requirements. (Para 12.5)

The Committee strongly recommends that the Ministry should direct CDSCO to send a stern warning to all manufacturers of new drugs to comply with mandatory rules on PSURs or face suspension of Marketing Approval. PSURs should be submitted in CDSCO-approved format which would help track adverse effects discovered in Indian ethnic groups. (Para 12.6)

13. PHARMACOVIGILANCE

The Committee feels that the conventional system of locating side effects through spontaneous reporting by doctors to either drug companies or drug regulators has been found to be unsatisfactory. The most effective system is by controlled post-marketing Phase IV studies on a very large number of patients. In the past decade, all the major adverse effects that led to banning of drugs were

identified in large scale Phase IV trials. The Ministry may wish to consider the possibility of using this format in the country. (Para 13.3)

14. UPDATION OF INFORMATION ON MARKETED DRUGS

14.3 The Committee feels that unless information on marketed drugs is continuously updated, there is risk of irrational or inappropriate use of medicines putting patients at risk. The Committee, therefore, recommends that immediate steps need to be taken to address this issue. The CDSCO should be directed to continuously update monographs based on information from regulatory authorities the world over. (Para 14.3)

15. SPURIOUS/SUB-STANDARD DRUGS

A drug can be categorized 'Not of Standard Quality' for a variety of both major and minor technical reasons such as not stating the name of the pharmacopoeia correctly, problem with quality of bonding agent, colouring agent, dissolution time, etc. However, there are other more serious cases, where the active ingredient is significantly less in quantity that can harm patients. Therefore, this problem needs to be addressed with all the seriousness that it deserves both by more rigorous checks in procuring bulk drugs (particularly from developing countries with not so stringent quality checks and export controls) and by in-house quality control by manufacturers or solving the problem in transportation and/or storage at distribution/retail levels. (Para 15.4)

By the time a sample is tested, a large number of packs get sold out with undeterminable injury to patients. There is no effective method of recalling unsold stocks lying in the distribution network. This cannot be allowed to go on. (Para 15.5)

The Committee feels that there should be severe punishment for manufacturing and for allowing sub-standard drugs to enter the distribution chain. Products with severe deficiencies should be penalized the same way as producers of spurious drugs by amending rules. There is also a case to incorporate penal provisions for manufacturing misbranded and adulterated drugs. (Para 15.6)

It is known that retail chemists also stock and sell items other than drugs including chocolates, cold drinks etc. During summer these items are stored in the refrigerator while due to paucity of space temperature-sensitive medicines may be lying outside. When samples are picked up, tested and found to be sub-standard, the State Drug Authorities blame and prosecute manufacturers. Therefore the Committee recommends that specifically in the case of temperature sensitive products such as insulins, due consideration should be given to the reference samples of the same batch preserved by the manufacturers. (Para 15.7)

The Committee is extremely anxious on both counts: such hugely costly imported drugs losing their potency before use and the possibility of fakes entering the chain. It is strange that multinational drug companies that have well staffed marketing offices in India, instead of importing drugs from their overseas affiliates and selling them are using traders to handle this activity. Apart from risk to patients, there is leakage of revenue to income tax. While the promotional expenses on imported formulations are being paid by the Indian branch of MNCs thus reducing income tax liability, there is no corresponding income since traders are paying directly to overseas offices of MNCs. The Committee would like the Ministry to ensure that in cases where MNCs have offices in India, traders are not permitted to import formulations of such companies. The Committee would like to be kept informed of the steps taken on this issue. (Para 15.9)

The Committee recommends that once a batch of a drug is found to be sub-standard and reported to CDSCO, it should issue a press release forthwith and even insert paid advertisements in the newspapers apart from uploading the information on the CDSCO website. Retail chemists should be advised to stop selling unsold stocks and return the same to local Drugs Inspectors as per rules. The Committee understands that at least two State Drug Authorities, that of Maharashtra and Kerala, have taken the initiative to upload information on spurious and sub-standard drugs on their websites on a monthly basis. These are welcome measures worth emulating by other states and the Centre.

(Para 15.11)

16. ADVERTISING OF PRESCRIPTION DRUGS IN THE LAY MEDIA

The Committee would like the Ministry to take appropriate action against the companies that have advertised the above Schedule H drugs in the lay press. The provisions in the Drugs and Magic Remedies Act are not stringent enough with the result that manufacturers violate them at will. It also recommends that apart from giving sharper teeth to the Drugs and Magic Remedies Act, a provision should also be incorporated in the Drugs and Cosmetics Rules to ban such practices and penalize offenders. The Committee would like to be informed of the action taken to implement these recommendations. (Para 16.2)

17. CONSUMER INFORMATION

The Committee is of the firm opinion that accurate information on drugs for patients is absolutely essential to prevent inappropriate use more particularly in children, elderly, during pregnancy and lactation. The Committee recommends that the matter may be looked into to ensure that consumers have the required information to use medicines safely. Given the widespread internet connectivity, it is advisable to devise a system where patients can get unbiased information on drugs at the click of the mouse in any language. (Para 17.3)

18. CLINICAL TRIALS ON NEW DRUGS

Due to the sensitive nature of clinical trials in which foreign companies are involved in a big way and a wide spectrum of ethical issues and legal angles, different aspects of Clinical trials need a thorough and in-depth review. This Committee has, accordingly, taken it up as a subject for detailed examination separately under the heading 'Clinical Trials of Drugs'. (Para 18.2)

List of Annexures

1. Clevudine

1. Copy of letter from **Dr. Randeep Guleria**, Professor of Medicine of All India Institute of Medical Sciences, New Delhi on **Clevudin**.
2. Copy of letter from **Dr. Satish Lahoti**, Professor of Medicine of K. B. N. Medical College, Gulbarga on **Clevudin**.
3. Copy of letter from **Dr. Appoorva Mukherjee**, Professor of Medicine of R. G. Kar Medical College, Kolkata on **Clevudine**.

2. Sertindole

- 1 Copy of letter from **Dr. M. Thirunavukarasu**, Professor and Head of the Department of Psychiatry of Stanley Medical College, Chennai on **Sertindole**
- 2 Copy of letter from **Dr. Lakshman Dutt**, Professor of SKP Psychiatric Nursing Home, Ahmedabad on **Sertindole**.
- 3 Copy of letter from **Dr. Nilesh Shah**, Professor and Head of the Department of Psychiatry of LTM Medical College, Mumbai. on **Sertindole**.

3. Doxofylline

- 1 Copy of letter from **Dr. Ashok Bajpai**, Professor of Medicine of M. G. M. Medical College, Indore on **Doxofylline**.
- 2 Copy of letter from **Dr. R.K. Mani**, Consultant, Indraprastha Apollo Hospital, New Delhi on **Doxofylline**.

4. Rivaroxaban

- 1 Copy of letter from **Dr. Rajesh Malhotra**, Professor of Orthopaedics, All India Institute of Medical Sciences, New Delhi on **Rivaroxaban**.
- 2 Copy of letter from **Dr. Sanjeev Mahajan**, Consultant at Dayanand Medical College, Ludhiana on **Rivaroxaban**.

- 3 Copy of letter from **Dr. Rajagopalan N.**, Professor of Orthopaedics, St. Johns Medical College, Bangalore on **Rivaroxaban**.

5. Ademetionine

- 1 Copy of letter from **Dr. Prabha Sawant**, Professor of the Department of Gastroenterology, Lokmanya Tilak Medical College, Mumbai on **Ademetionine**.
- 2 Copy of letter from **Dr. K.R. Vinaya Kumar**, Professor of Gastroenterology, Medical College Thiruvananthapuram on **Ademetionine**.
- 3 Copy of letter from **Dr. Abhijit Chowdhury**, Professor and Head of the Digestive and Liver Diseases, IPGMER, Kolkata on **Ademetionine**.
- 4 Copy of letter from **Dr. Anil Arora**, Chairman and Chief of Hepatology Services, Sir Ganga Ram Hospital, New Delhi on **Ademetionine**.

6. Pirfenidone

- 1 Copy of letter from **Dr. Randeep Guleria**, Professor of Pulmonary Medicine, AIIMS, New Delhi **dated 19th June, 2010** on **Pirfenidone**.
- 2 Copy of letter from **Dr. P. Prabhudesai**, Consultant Chest Physician, Lilavati Hospital, Mumbai dated **May 25, 2010** on **Pirfenidone**.
- 3 Copy of letter from **Dr. Dheeraj Gupta**, Additional Professor of Pulmonary Medicine, PGI, Chandigarh dated **14th June, 2010** on **Pirfenidone**.
- 4 Copy of letter from **Dr. Vijai Kumar R.**, Pulmonologist of Yashoda Hospital, Secunderabad dated **12th June 2010** on **Pirfenidone**.

7. Dapoxetine

- 1 Copy of letter from **Dr. Hemant R. Pathak**, Professor and Head, Department of Urology, T. N. Medical College, Mumbai dated **25-3-2010** on **Dapoxetine**.
- 2 Copy of letter from **Dr. Nilesh Shah**, Professor and Head, Department of Psychiatry, L. T. M. Medical College, Mumbai dated **19-3-2010** on **Dapoxetine**.
- 3 Copy of letter from **Dr. Dilip Karmakar**, Professor and Head, Department of Urology, Calcutta National Medical College, Kolkata dated **24-2-2010** on **Dapoxetine**.

8. Nimesulide injection.

- 1 Copy of letter from **Dr. S. H. Talib**, Professor and Head, Department of Medicine, Government Medical College, Aurangabad dated **17-8-2005** on **Nimesulide Injection**.

- 2 Copy of letter from **Dr. Raju Vaishya**, Sr. Consultant Orthopaedic Surgeon, Indraprastha Apollo Hospital, New Delhi dated **17-6-2005** on **Nimesulide Injection**.

9. FDC of Aceclofenac with Drotaverin

- 1 Copy of letter from **Dr. Promila Pandhi**, Professor & Head, Department of Pharmacology, PGI, Chandigarh on **FDC of Aceclofenac with Drotaverine**.
- 2 Copy of letter from **Dr. Kalpana Ernest**, Professor & Head, Department of Pharmacology & Clinical Pharmacology, Christian Medical College, Vellore. on **FDC of Aceclofenac with Drotaverine**.
- 3 Copy of letter from **Dr. Satish B. Dharap**, Professor of Surgery, L. T. M. Medical College, Mumbai on **FDC of Aceclofenac with Drotaverine**.
- 4 Copy of letter from **Dr. D. Arvind Kumar**, Professor of Medicine, Gandhi Medical College, Secunderabad. on **FDC of Aceclofenac with Drotaverine**.
- 5 Copy of letter from **Dr. Pramod Kumar Mallick**, Professor and Head of Postgraduate Department of Surgery, S. C. B. Medical College, Cuttack. on **FDC of Aceclofenac with Drotaverine**.
- 6 Copy of letter from **Dr. B. Prahlad**, Professor of Medicine and Civil Surgeon, Gandhi Medical College, Secunderabad on **FDC of Aceclofenac with Drotaverine**.

10. Deanxit Product Insert

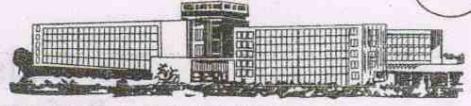
11. Placentrex: copy of letter from DCGI to Albert David Ltd, Calcutta.

12. Baralgan Product Insert

13. Deanxit advertisement in Times of India.

73

Department of Medicine
All India Institute of Medical Sciences
Ansari Nagar, New Delhi-110 029



Dr. Randeep Guleria
MD, DM (Pulmonary Medicine), MNAMS
Professor

Tel Off. : 011-26593676
Tel. Res. : 011-26198654, 011-26195447
Fax : 91-11-26588663, 26589732
E-mail : randeepg@hotmail.com
randeepguleria2002@yahoo.com

AD (CP)

9262
18/11/09

21st October 2009

Mr. A.B. Ramteke,
Directorate General of Health Services
FDA Bhavan, Kotla Road,
New Delhi - 110 003.



AD
17/11
TD (M)

Sub: Expert Opinion on Clevudine 30 mg Capsules

Dear Mr. Ramteke,

This reply is in response to your letter 12-174/08-DC dated 16/04/2009. I have gone through the literature on the said product and feel that, this product will be a good additional drug for inhibition of viral replication and treatment of patient chronic hepatitis B infections.

Based on the literature provided and keeping in view the safety & efficacy of the drug clevudine, in my opinion, permission may be granted without conducting clinical trials in Indian patients.

With best regards,

Thanking you,

(Randeep Guleria)

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Date: 15/10/09

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18/11/09

ADCCP

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19/11/09

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17/11
TOLCUM

To,
Mr. A.B. Ramteke
Directorate General of Health Services
FDA Bhavan, Kolta Road
New Delhi

Subject: Expert Opinion on Clevudine 30mg Capsules

Dear Mr. Ramteke,

This reply is in response to your letter 12-174/08-DC dated 16/04/2009. I have gone through the literature on the said product and is very much convinced, this will be a very good value addition drug for inhibition of viral replication and treatment of chronic hepatitis B patients.

Based on my review of the provided literature and keeping in view the safety & efficacy of the drug clevudine, in my opinion permission may be granted to the company even without conducting the clinical trials in Indian patients.

I thank you for giving me this opportunity to review the said molecule.

Thanking you.

With Best Regards,

Amrta
15/10/09

Dr. Appoorva Mukherjee
Prof. Dept. of Medicine
R.G Kar Medical College Kolkata
Prof. & Head of Dept.
of Medicine
R. G. Kar Medical College & Hospital
Kolkata

70

Dr. Satish Lahoti MD
Professor of Medicine
K.B.N. Medical College, Gulbarga – 585 102

Date: 13th Oct. 2009.

9266
18/11/09

Accd

Dr
17/11
TOLUN

To,
Mr. A.B. Ramteke
Directorate General Of Health Services,
FDA Bhavan, Kolta Road,
NEW DELHI



Sub: Expert Opinion on Clevudine 30mg Capsules

Dear Mr. Ramteke

This is with reference to your letter No. 12-174/08DC/dated/ 15/04/2009. After extensive study of literature provided to me and referring to Internet I have come to the conclusion that this drug will prove to be beneficial to our Indian Patients and will be of grate help to our physicians to fight the Hepatitis B Infection.

After extensive study of the subject material and keeping in view efficacy and safety of the drug clevudine, I am of the opinion that the company may be permitted even without conducting clinical trails in Indian patients.

I thank you for giving me the opportunity to review the molecule.

Thanking you

With Best Regards,

Dr. Satish Lahoti MD
Prof. Dept. of Medicine
KBN Medical College
Gulbarga (Karnataka State)

संस्थान से दिव्यी मंत्रों का स्वागत है

①

भेषजवृत्त विज्ञान विभाग

स्नातकोत्तर चिकित्सा शिक्षा एवं अनुसंधान संस्थान, चण्डीगढ़ - १६००१२ (भारत)

DEPARTMENT OF PHARMACOLOGY
POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH, CHANDIGARH - 160 012 (INDIA)
दूरभाष/Ph.(O):0172-2743451, 2756761, 2755241, (R): 2727354, फैक्स/Fax: 0172-2743451, 2744401, टेलीग्राम/Telex:0396-735 PCIIN
ई-मेल/E-mail:ppandhi17@hotmail.com, Gram: POSTGRADMED

डॉ० (श्रीमती) प्रोमिला पांधी
प्राध्यापक एवं अध्यक्ष



Dr. (Mrs.) Promila Pandhi
M.D., D.M. (Clin, Pharm), MNAMS, FCP
Professor & Head

संख्या/No./Pharma- 07/259
दिनांक/Dated..... 1.3.67

To,
Themis Medicare Pvt. Ltd.,
11/12, Udyog Nagar,
S.V. Road,
Goregaon (W),
Mumbai.

Sub: Expert opinion for fixed dose combinations of drotaverine (80 mg) plus aceclofenac (100 mg) tablets.

I have studied the data provided by Themis Medicare Limited as regards the Fixed Dose Combination of drotaverine (80 mg) plus aceclofenac (100 mg) tablets for the use in conditions like Control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colic, cholecystopathy associated with spastic symptoms, cholelithiasis, cholecystitis, nephrolithiasis, peripheral arteries spasm, myometrium hyperactivity, smooth muscle spasms due to instrumental diagnostic procedures and neck of uterus spasm during delivery.

Drotaverine, a phosphodiesterase IV inhibitor, has an antispasmodic action without the antimuscarinic side-effects. It is currently used successfully in many countries for treating renal colic.

Aceclofenac, a phenylacetic acid derivative (2-((2,6-dichlorophenyl)amino)Phenylacetooxyacetic acid) related to diclofenac. It is a novel NSAID indicated for the symptomatic treatment of pain and inflammation.

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDS have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

The information provided with experimental & clinical references to Pharmacological actions and rationale seems to suggest that the combination would have added benefits to the patient. So in my opinion the combination of Drotaverine and aceclofenac would provide an effective pain relieving therapy.

1165
418/10
Prof. M. Thirunavukarasu, M.D.(Psy), D.P.M.,
Professor and Head, Department of Psychiatry
Star Medical College and Hospital
Chennai - 600 001, Tamil Nadu
Phone: +91 44 25281346

Member, The Senate & Member, The Governing Council
Tamil Nadu, Dr. M.G.R. Medical University, Chennai
President Elect-Indian Psychiatric Society

To:

Date:

The Drugs Controller General of India
FDA Bhavan
CHEB Campus
Kotla Road
New Delhi 110002

Chennai
5/05/2010

Dear Sir,

Subject: Sertindole Tablets
Ref: Your letter F. No. 12-67/C9- DC dated 5th March 2010

I thank you for your request to seek my opinion regarding essentiality and desirability of the product Sertindole for India vide your letter F. No. 12-67/09- DC dated 5th March 2010.

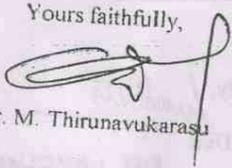
I have gone through the published literature and India specific clinical study report for Sertindole. Sertindole is known to cause QT prolongation in ECG. However the study doesn't reveal that it has a pathological effect on the cardiac status on the patient. It is mentioned that there is history of Intrauterine Death if mother takes Sertindole in the 1st/2nd trimester. It is noted that there is increased adverse effects when the dose exceeds 10mg/day. The effective therapeutic dose however is 12-20mg/day.

Schizophrenia is a disease which is chronic in nature & debilitating to the individual. Although many drugs are available, one third of the patients need new interventions with newer drugs.

Keeping the above facts in mind, the efficacy of Sertindole cannot be ignored. So, the advantage of the molecule will be useful to our patients with Schizophrenia but a warning about the Pre Drug Assessment of Cardiac Status is a must and caution must be exercised when administering the drug to women of childbearing age.

Thanking you,

Yours faithfully,


Dr. M. Thirunavukarasu

Address for Communication:

1018 A, Sixth Avenue, Anna Nagar
Chennai - 600 040
Tel: +91 44 26187688 Fax: +91 44 26610959
E-mail: drmrthiru@yahoo.com

Clinic:

18-A, Flowers Road, Kilpauk
Chennai 600 010
Tel: +91 44 26411242 / 26430437
Mobile: 94440 34647

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26/4/10

77

DR Nilesh Shah
Prof. & H.O.D,
Psychiatry-OPD-21.
LTMMC<MGH
Sion, Mumbai-022.

Date: 17/04/2010

To
The Drugs Controller General of India
FDA Bhawan,
CHEB Campus,
Kotla Road
New-Delhi-110002

Dear Sir,

Subject: Sertindole Tablets

Reference: (i) Letter F.No.12-67/09-DC dated 5th March 2010

I thank DCGI for the request to seek my opinion regarding essentiality and desirability of the product Sertindole for Indian patients vide your letter no: F.No.12-67/09-DC dated 5th March 2010.

The published literature and India specific Clinical Study Report for Sertindole confirms the suitability for Indian patients.

I feel that Sertindole is an effective, non-sedating antipsychotic with placebo-like extra pyramidal symptoms (EPS) which is an advantage in patients with schizophrenia.

Moreover the clinical study on 460 Indian patients has also shown that all-cause mortality for Serdolect was low and there was no death reported due to cardiac events.

Serdolect was also well tolerated in Indian patients and treatment duration was shorter in the sertindole group compared to Risperidone group.

Like many other antipsychotic drugs, sertindole may causes prolongation of QTc intervals in ECG. Therefore clinicians may have to monitor the QTc intervals of their patients when this drug is prescribed. From the benefits of the molecule, I feel that Serdolect should be useful to Indian patients with schizophrenia.

My view is that Serdolect will be useful for Indian patients and an added antipsychotic with good tolerability and the DCGI should consider this for India.

Thanking You,

Yours Faithfully,
Dr. Nilesh Shah

Nilesh Shah
17.4.10

Dr. Nilesh Shah
Professor & Head,
Department of Psychiatry
L.T.M.C. & L.T.M.G.H.
Sion Hospital-Sion, Mumbai-400 022

Dr. Ashok Bajpai -

M.D. (Medicine), D.T.C.D., M.C.A.I.

डॉ. अशोक बाजपाई

एम.डी. (मेडिसिन), डी.टी.सी.डी., एम.सी.डी.आई.

M.D. (Medicine) - Professor & HOD of Medicine - M.G.M. Medical College - M.Y. Group Hospitals, INDORE (M.P.)
• Chest Physician, Consultant in, Critical Care Medicine
चेस्ट फिजिशियन • कन्सल्टंट इन क्रिटिकल केयर मेडिसिन • मानद फिजिशियन : गीता भवन हॉस्पिटल

Date : 26th Aug 2004

To,
The Drug Controller of India.
DGHS
Nirman Bhawan,
NEW DELHI -11.

Ref. : Letter F.No. (12-03/2004 - DC dated 31st May, 2004.)

Sub. : Permission to manufacture & market Doxophylline.

Sir,

With reference to above I thank you for asking me to evaluate the literature of Doxophylline.

Doxophylline is a newer methylxanthine which is comparable in efficacy with conventional methylxanthines. Advantages of Doxophylline is reduced incidence of side effects particularly with respect to the central nervous system, cardiovascular and gastrointestinal system. This drug (Doxophylline) may be permitted to manufacture and market in India.

Thanking you.

With Regards.

Dr. Ashok Bajpai

Address: St. Charles Hospital, Alankar Point, Opp. Rajwade Museum, Besa & Bhowan Road, INDORE Phone: 2492230

Office: M. S. D. P. C. - Bundys, Lalpur. Phone: 2492230, 2492231, 2492232

Home: 2492230, 2492231, 2492232 Phone: 2492230, 2492231, 2492232 Phone: 24924514

Dr. R. K. Mani M.D., M.R.C.P. (UK)
Senior Consultant in Respiratory Medicine,
Intensive Care & Sleep Medicine

**INDRAPRASTHA
APOLLO
HOSPITALS**



O.P.D. Time (Room No. : 1217)

Mon., Tue., Fri. : 12.00 noon - 4.00 p.m.
Wed. Thu. : 8.00 a.m. - 12.00 noon

Date: 6th Aug 2004

To

The Drug Controller General of India
DGHS
New Delhi

Sir,

I have received the relevant literature concerning the drug, Doxofylline. It is a newer methylxanthine which is comparable in efficacy with the conventional methylxanthines. There is an added advantage of reduced incidence of side effects particularly with respect to the central nervous system, cardiovascular and gastrointestinal systems. Animal experiments and clinical trials have borne out these facts.

This drug (Doxofylline) may therefore be a useful addition to the existing pharmacopia.

Thanking you

With regards

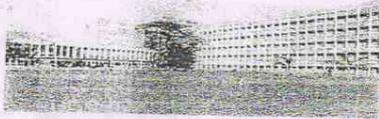
Dr. R.K Mani
Visiting Consultant
Indraprastha Apollo Hospitals
New Delhi

WORLD CLASS HEALTHCARE

Apollo Hospital Sarita Vihar, Delhi-Mathura Road, New Delhi-110 044 (India)
Ph. : 26825801, 26825858 Extn 1217, 1270, 1271 • Fax : 91-11-26823629, 26828704

Residence

C-80 Neel Enclave, Khar Gaon Marg, New Delhi-110049 Tel. : 26516059, 26060010
Fax: 91-11-26117116, E-mail: rkmjs@vsnl.net



Professor Rajesh Malhotra MBBS, MS, NASI
Delhi-27
Consultant Orthopaedic Surgeon
Fellow in Bone & Cartilage Transplantation
& Revision Joint Replacement Surgery, Princess

Resi.: S-25, IInd Floor, Rajouri Garden New

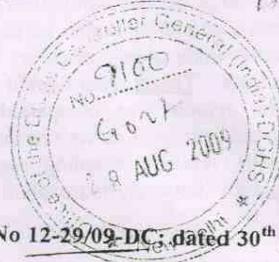
Tel.: 25432252, 25109729
Email: rmalhotra62@hotmail.com
Office: 91-1126588700 / 26588500 (Ext: 3589)

7168
01/09/09

DDP/M 04.08.2009

To

The Drugs Controller General of India
FDA Bhawan,
CHEB Campus
New Delhi - 110002



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12/9/9
TDAC

Subject: **Rivaroxaban 10mg film coated tablet (F.No 12-29/09-DC, dated 30th July 2009**

I would like to apprise you of the current Indian Scenario regarding venous thromboembolism. Venous thrombosis may occur in more than 50% of patients undergoing surgical procedures, particularly those involving the hip and knee; and 10% to 40% of patients who undergo abdominal or thoracic operations. Prophylactic treatment especially Low molecular weight heparins (LMWHs) is recommended in Indian patients undergoing major joint surgeries (hip and knee replacement surgeries)

Low molecular weight heparins (LMWHs) remain the mainstay of VTE prophylaxis presently. The low molecular weight heparins (LMWHs) were developed and introduced in 1980s. LMWHs do not require monitoring and have a lower risk of HIT, but they must be administered by injection, and can accumulate in patients with kidney impairment. One of the mainstays of current treatment, enoxaparin, first emerged in 1987.

Enoxaparin provides effective and safe VTE prophylaxis; however it needs to be administered subcutaneously which is often associated with pain, subcutaneous bruising, oozing, and hematoma. Although rare, Enoxaparin may trigger heparin-induced thrombocytopenia.

Rivaroxaban

Rivaroxaban (BAY 59-7939) is a novel selective inhibitor of the serine protease coagulation Factor Xa (FXa). The drug has been developed for the prophylaxis of venous thromboembolism.

Rivaroxaban has following benefits over existing therapy

- ✓ 1. Convenient use both in and out of hospital
- ✓ 2. Safe and effective regulation of coagulation from the first dose and throughout therapy
- ✓ 3. Broad safety margin across a wide range of effective doses
- ✓ 4. Fixed doses for the majority of patients provide predictable outcomes without the need for dose adjustment
- ✓ 5. No need for laboratory monitoring saves healthcare costs, through fewer hospital/physician visits, and patients' time

Indian data with Rivaroxaban

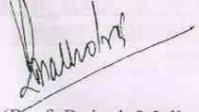
✓ A Prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multicenter, and multinational trial was conducted in India with 15 investigators in patients undergoing elective total knee replacement. A total of 495 Indian subjects were randomized; 486 subjects were treated with study drug (safety population). Of these, 228 subjects were valid for the modified intent to treat (MITT) analysis and 226 subjects were valid for the per protocol (PP) analysis.

✓ In this large double-blind study, oral administration of rivaroxaban 10 mg od was both effective and comparable to enoxaparin 30 mg SC bid in the prevention of VTE in subjects undergoing elective TKR. Rivaroxaban met the pre-specified efficacy objectives. The clinical benefit of rivaroxaban was accompanied by a favorable safety profile, which was comparable to enoxaparin in terms of adverse event rates, treatment-emergent as well as during follow-up. The incidence of major and non-major clinically relevant bleeding events as well as all bleeding events was numerically comparable between rivaroxaban and enoxaparin groups.

✓ The efficacy and safety results of this study provide evidence for the net clinical benefit of rivaroxaban in the prevention of VTE for subjects undergoing elective TKR.

To summarize, considering the unmet medical need for VTE prevention, drawbacks of existing therapy and the clinical benefits of Rivaroxaban with equivalent safety profile compared to existing therapies makes Rivaroxaban an excellent clinical choice. The drug has undergone clinical trials in India and the benefits of Rivaroxaban should be available to Indian patients at the earliest. This will help us in better management of DVT in patients undergoing hip and knee replacement surgeries.

Thanking you,
Yours sincerely,



(Prof. Rajesh Malhotra)

DR. RAJESH MALHOTRA
M.B.B.S., M.S.
Professor of Orthopaedics
All India Institute of Medical Sciences
New Delhi

24

JAYANAND MEDICAL COLLEGE & HOSPITAL LUDHIANA

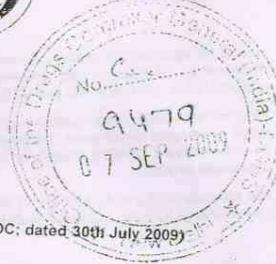


7552
18/09/09

Ref. No. DMCH/ _____

Dated 18/09/09

The Drugs Controller General of India
FDA Bhawan,
GHEB Campus
New Delhi -110002



Handwritten notes: A/C 1319, TOA, etc.

Subject Rivaroxaban 10mg film coated tablet (F.No 12-29/09-DC; dated 30th July 2009)

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common cause of cardiovascular mortality and morbidity. Several studies have also shown that DVT has important economic consequences. The average discounted lifetime cost of DVT complications following total hip replacement has been estimated to be approximately \$3000. Furthermore, in patients undergoing any type of MOS, those who developed a clinical VTE following hospital discharge had a 3.4-day average increase in hospitalization days, coinciding with a \$6000 average increase in medical charges when assessed 90 days post surgery.

Venous thrombosis may occur in more than 50% of patients undergoing surgical procedures, particularly those involving the hip and knee; Prophylactic treatment is recommended in Indian patients undergoing major joint surgeries (hip and knee replacement surgeries).

Low molecular weight heparins (LMWHs)

LMWHs unlike heparin do not require monitoring and have a lower risk of HIT, but they must be administered by injection, and can accumulate in patients with kidney impairment. One of the mainstays of current treatment, enoxaparin, first emerged in 1987.

Enoxaparin provides effective and safe VTE prophylaxis, however it needs to be administered subcutaneously which is often associated with pain, subcutaneous bruising, oozing, and hematoma. Although rare, Enoxaparin may trigger heparin-induced thrombocytopenia.

Rivaroxaban

Rivaroxaban is a novel selective inhibitor of the serine protease coagulation Factor Xa (FXa). The goal with respect to rivaroxaban was to develop an oral, direct-acting, antithrombotic agent with a wide therapeutic window, good safety and efficacy, a simpler route of administration, and in general without any need for dose-adjustment and monitoring.

Rivaroxaban an oral anticoagulant has following benefits over existing therapy; Convenient use both in and out of hospital; Safe and effective regulation of coagulation from the first dose and throughout therapy; Broad safety margin across a wide range of effective doses; Fixed doses for the majority of patients provide predictable outcomes without the need for dose adjustment; No need for laboratory monitoring saves healthcare costs, through fewer hospital/physician visits, and patients' time

Indian data with Rivaroxaban

To determine the efficacy and safety of Rivaroxaban in Indian patients 495 patients were enrolled in a Prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multicenter, and multinational trial. This study was conducted in India with 15 investigators in 495 patients undergoing elective total knee replacement.

A total of 495 Indian subjects were randomized; 486 subjects were treated with study drug (safety population). Of these, 485 subjects were valid for the modified intent to treat (mITT) analysis and 226 subjects were valid for the per protocol (PP) analysis.

In this large double-blind study, oral administration of rivaroxaban 10 mg od was both effective and comparable to enoxaparin 20 mg SC bid in the prevention of VTE in subjects undergoing elective TKR. For both the PP and mITT populations, the incidence rate of major VTE in the enoxaparin 20 mg bid group was more than the rate observed in the rivaroxaban 10 mg od group. For both populations, confidence intervals for efficacy endpoints (as assessed by

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Administrative footer text including contact information for the hospital and regulatory details.

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DAYANAND MEDICAL COLLEGE & HOSPITAL LUDHIANA

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Ref. No. DMCH/ _____

Dated 18/8/1

central adjudication committee), establishes that rivaroxaban 10 mg od is comparable to enoxaparin 30 mg bid. Thus, rivaroxaban 10 mg od was non-inferior to enoxaparin 30 mg bid in preventing major VTE (the composite of proximal DVT, non-fatal PE and VTE-related death).

The clinical benefit of rivaroxaban was accompanied by a favorable safety profile, which was comparable to enoxaparin in terms of adverse event rates, treatment-emergent as well as during follow-up. The incidence of major and non-major clinically relevant bleeding events as well as all bleeding events was numerically comparable between rivaroxaban and enoxaparin groups.

The efficacy and safety results of this study provide evidence for the net clinical benefit of rivaroxaban in the prevention of VTE for subjects undergoing elective TKR.

Reference

1. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD, RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet*. 2009 May 16;373(9676):1673-80. Epub 2009 May 4.
2. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Sogliani AG, Pap AF, Misselwitz F, Haas S, RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet*. 2009 Jul 5;372(9632):31-9. Epub 2008 Jun 24.

Thus to conclude, in view of limitations of existing drugs for DVT & PE, the unmet medical need for VTE prevention, and the clinical benefits of oral Rivaroxaban with equivalent safety profile compared to existing therapies makes Rivaroxaban an excellent choice in clinical practice. Since the drug has undergone clinical trials in India no further study are necessary at this point of time. Rivaroxaban should be made available to Indian patients & for use by orthopaedic fraternity at the earliest. This will help orthopaedicians use rivaroxaban for better prophylactic treatment for prevention of DVT in patients undergoing hip and knee replacement surgeries.

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 Phone No : 4687700 Ext. 7501
 Medical Dept. : 4687700 Ext. 7504, 7229
 Fax : Academic : 37700 Ext. 7503

EPABN : 46877004301700s
 Fax : 0161-2302626
 Internet : dmchldh@gidc.com
 Website : www.dnml.edu



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To

17 Aug 2009

Mr. A.K. Pradhan
Asst. Drugs Controller (I)
For Drugs Controller General (India)
FDA Bhawan,
CHEB Campus
New Delhi - 110002

7217
04/09/09

(11)

Subject: Rivaroxaban 10mg film coated tablet (F.No 12-29/09-DC; dated 30th July 2009)

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common cause of cardiovascular mortality and morbidity. Subjects undergoing major orthopedic surgery, which includes hip and knee arthroplasty, represent a group that is at particularly high risk for VTE.

Venous thrombosis may occur in more than 50% of patients undergoing surgical procedures, particularly those involving the hip and knee; Prophylactic treatment is recommended in Indian patients undergoing major joint surgeries (hip and knee replacement surgeries).

DTIs and indirect Factor Xa inhibitors

Fondaparinux introduced recently, is an indirect Factor Xa inhibitor and has been shown to be effective. However it is also administered by injection, which is inconvenient when long-term use is required.

Direct thrombin inhibitors (DTIs) were first introduced in the 1990s. DTIs inhibit the action of thrombin, the enzyme that promotes clot formation. Ximelagatran, the first oral DTI, was not approved in the U.S. and was withdrawn from the European market in 2006 primarily due to severe liver injuries in some patients.

Low molecular weight heparins (LMWHs)

✓ The low molecular weight heparins (LMWHs) were developed and introduced in 1980s. LMWHs do not require monitoring and have a lower risk of HIT, but they must be administered by injection, and can accumulate in patients with kidney impairment. One of the mainstays of current treatment, enoxaparin, first emerged in 1987.

✓ Enoxaparin provides effective and safe VTE prophylaxis; however it needs to be administered subcutaneously which is often associated with pain, subcutaneous bruising, oozing, and hematoma. Although rare, Enoxaparin may trigger heparin-induced thrombocytopenia.

Rivaroxaban

✓ Rivaroxaban (BAY 59-7939) is a novel selective inhibitor of the serine protease coagulation Factor Xa (FXa). The drug has been developed for the prophylaxis of venous thromboembolism.

Handwritten signatures and dates: 29/09, 29/09, 29/09, 29/09

Rivaroxaban has following benefits over existing therapy

1. Convenient use both in and out of hospital
2. Safe and effective regulation of coagulation from the first dose and throughout therapy
3. Broad safety margin across a wide range of effective doses
4. Fixed doses for the majority of patients provide predictable outcomes without the need for dose adjustment
5. No need for laboratory monitoring saves healthcare costs, through fewer hospital/physician visits, and patients' time

Indian data with Rivaroxaban

To determine the efficacy and safety of Rivaroxaban in Indian patients, A Prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multicenter, and multinational trial was conducted in India with 15 investigators in patients undergoing elective total knee replacement.

A total of 495 Indian subjects were randomized; 486 subjects were treated with study drug (safety population). Of these, 228 subjects were valid for the modified intent to treat (MITT) analysis and 226 subjects were valid for the per protocol (PP) analysis.

In this large double-blind study, oral administration of rivaroxaban 10 mg od was both effective and comparable to enoxaparin 30 mg SC bid in the prevention of VTE in subjects undergoing elective TKR. For both the PP and MITT populations, the incidence rate of major VTE in the enoxaparin 30 mg bid group was more than the rate observed in the rivaroxaban 10 mg od group. For both populations, confidence intervals for efficacy endpoints (as assessed by central adjudication committee), establishes that rivaroxaban 10 mg od is comparable to enoxaparin 30 mg bid.

Thus, rivaroxaban 10 mg od was non-inferior to enoxaparin 30 mg bid in preventing major VTE (the composite of proximal DVT, non-fatal PE and VTE-related death).

The clinical benefit of rivaroxaban was accompanied by a favorable safety profile, which was comparable to enoxaparin in terms of adverse event rates, treatment-emergent as well as during follow-up. The incidence of major and non-major clinically relevant bleeding events as well as all bleeding events was numerically comparable between rivaroxaban and enoxaparin groups.

The efficacy and safety results of this study provide evidence for the net clinical benefit of rivaroxaban in the prevention of VTE for subjects undergoing elective TKR.

Since the drug has undergone clinical trials in India no further study are necessary at this point of time.

7

DEPARTMENT OF GASTROENTEROLOGY

**LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE
AND**

LOKMANYA TILAK MUNICIPAL GENERAL HOSPITAL

Sion, Mumbai-400 022, INDIA.
Phone : 2401 5799, 2407 6381 - 90, Ext. 244/246 • Fax : 2407 6100

Date : 11.3.2010.

To,

Directorate General of Health Services,
Office of Drugs Controller General (India),
New Delhi

8

Cifer

Sub : Ademetionine Tablets 200/400mg
Ref : Your letter F.No.12-55-10-DC dtd 9.8.2010.

Sir,

Kindly refer to your letter seeking my expert opinion on the essentiality and desirability of Ademetionine in the country, as well as requirement of conducting clinical trials with Ademetionine tablets before grant of marketing authorization in the country.

Currently, SAME is available in India as a dietary supplement and is used in multiple conditions including liver diseases.

SAME as a drug is used in various conditions since the last 20 years and has been marketed in several European countries as well as in the US.

Sufficient and robust clinical data is available establishing the efficacy and safety of SAME in intrahepatic cholestasis and liver disease.

Currently, there are very few drugs available for the management of intrahepatic cholestasis and liver disease. After evaluating the data on SAME, it is essential and desirable to have this drug in the Indian market.

The drug has a good safety profile. However post marketing surveillance studies can be carried out.



Dr. Prabha Sawant,
Prof. & Head, Dept. of GI,
LTMGC & LTH, Sion, Mumbai.
DR. PRABHA SAWANT, FRCG, FRCR,
Prof. & Head, Dept. of Gastroenterology,
LTM.M. College & LTH, Sion Hospital,
Sion, MUMBAI-400022

8
Dr. K.R. Vinaya Kumar

M.D(Gen Med), D.M(Gastro), MRCP(UK), FRCP(London)

Vice Principal, Professor & Head, Department of Gastroenterology

Kattoor, ARRA No 14

Medical College, Trivandrum

Avitam Road, Kumarapuram

Trivandrum-695011

Phone Res: 0471-25556880

Member PG Board & Faculty of Medicine

e-mail vinayakumar@sify.com

Kerala University.

Course Director, MRCP

Phone 0471-2528241(Hospital)

0471-2528241(Dept)

To,

Directorate General of Health Services

Office of Drugs Controller General (India)

New Delhi

Sub : Your letter F.No.12-55/10-DC dated 9th August 2010

Sir,

Thank you for your letter dated 9th August 2010 seeking my opinion on Ademetonine (SAME) tablets 200/400 mg.

On perusal of the appended literature, it is evident that SAME is available in International markets since many years. The pharmacodynamic properties of exogenous SAME have been widely investigated and a large number of studies and reviews have been published in established international journals. The efficacy and safety of SAME has been well validated in the studies.

In India, current treatment options in the management of intrahepatic cholestasis and liver diseases are limited and there exists a need to introduce a drug that has proven efficacy and safety.

In light of the evidence presented on SAME, it is indeed extremely essential and desirable that this drug be made available in the Indian market immediately, without going through the clinical trial process.

Yours Truly

Dr. K.R. Vinaya Kumar

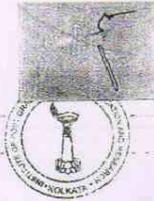
Dr. K.R.V. KUMAR, M.D, D.M, M.R.C.P.
Register No : 9575
Professor of Gastroenterology
Medical College, Thiruvananthapuram.

State of Post Graduate
Medical Education & Research

Dr. Acharya J.C. Bose Road

Dr. Abhijit Chowdhury, M.D., D.M.

Professor & Head
Department of Digestive & Liver Diseases



Kolkata-700 020, West Bengal, India

E-mail - achowdhury2002@yahoo.co.in

To,
Directorate General of Health Services
Office of Drugs Controller General (India)
New Delhi

Sub : Ademetionine Tablets 200 / 400 mg

Sir,

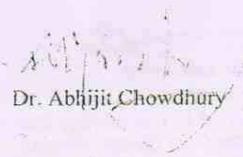
I am in receipt of your letter dated 9th August 2010.

I am extremely glad that your Directorate is considering the introduction of Ademetionine (SAME) tablets in India.

On the basis of the evidence presented, SAME has established the safety and efficacy as demonstrated by several clinical studies and reviews presented over the last 20 years. SAME is also currently available in many countries, both as a drug and dietary supplement.

Definite treatment gaps exist in India currently in the management of intrahepatic cholestasis and liver diseases. Availability of a drug like SAME will not only strengthen the treatment armamentarium of the doctors managing these conditions but is also extremely essential.

Based on the wealth and evidence already presented on SAME, I would like to recommend that this drug be introduced in the Indian market without any further clinical trials.


Dr. Abhijit Chowdhury



Sir Ganga Ram Hospital
 C-2E/62, Pusa, No. 1-20, 1st Floor, 4, B p.m. (Mon. - Fri.)
 Tel: 011-42257547/55700

DM (Gastro), AAIMS, FIMS, FRCP (Edinburgh)
 Sr. Gastroenterologist, Therapeutic Endoscopist &
Chief of Hepatology Services
Sir Ganga Ram Hospital
 Visiting Fellow, Queen Elizabeth Hospital Birmingham (U.K.)

Noble Medicare
 C-2E/62 A, Janakpuri, New Delhi-58
 Tel: 35592743, 26673442, 25614743, 45523361
 Sat. 12 Noon (Mon. - Sat. Except Tue.)
 B. No. 9.00 p.m. (Mon. - Fri.)
 e-mail: dr.anil.arora50@gmail.com

To,
 Directorate General of Health Services
 Office of Drugs Controller General (India)
 New Delhi) 9

Sub : Ademetionine Tablets 200/400mg
Ref : Your letter F.No.12-55/10-DC dated 9 August 2010

Sir,

This is with reference to your letter dated 9th August 2010 and the literature presented along with.

SAME is available in many European countries and in the US since the last 20 years. World wide studies with Same have been conducted that have demonstrated its efficacy and safety. The existing clinical data available also shows that this product has no side effects and is an effective agent in the management of intrahepatic cholestasis and liver diseases.

Currently in India, with the limited treatment options available in managing these conditions, it is essential that a drug like SAME be introduced at the earliest

Having been backed by adequate published evidence of usage experience internationally, I would like to recommend its introduction in the Indian market without further delay and without having to undergo any additional clinical trials.


 Dr. Anil Arora
 Chairman
 Chief of Hepatology Services
 Dept. Of Gastroenterology
 Sir Ganga Ram Hospital
 New Delhi



Dr. Randeep Guleria
MD, DM (Pulmonary Medicine), MNAMS
Professor

Tel Off. : 011-26593676
Tel. Res. : 011-26198654, 011-26195447
Fax : 91-11-26588663, 26589732
E-mail : randeepg@hotmail.com
randeepguleria2002@yahoo.com
19th June 2010

Mr. A. K. Pradhan
Asst. Drugs Controller General (India)
FDA Bhavan,
Kotla Road
New Delhi

Dear Mr. Pradhan,

This is with reference to your letter No. F.No. 12-262/09-DC (Pt.A), dated 20th May 2010 on my opinion regarding Pirfenidone. I have the following observations and comments to make:

- Idiopathic Pulmonary Fibrosis (IPF) is a debilitating and progressive fibrotic disease of the lungs with a median survival of about 3 to 5 years once a diagnosis is made. Managing these patients can be difficult and challenging. The diagnosis is difficult to make and one relies on a clinico-radiological profile for a diagnosis. A definite diagnosis requires a surgical lung biopsy which is often difficult to do in these sick patients.
- Currently, there is no definite therapy that has been approved to be used for the treatment of IPF and which can significantly benefit these patients. Current 'Conventional therapy' used in these patients consists of a combination of corticosteroids with immunosuppressives such as azathioprine which are of unproven benefit and in some patients may be associated with serious toxicities. No survival benefit has been shown with these agents in studies. Recently high doses N-acetyl cysteine, an antioxidant drug have been used but has not yet been approved for the same.
- Several new agents have been studied of which pirfenidone is one of them. In recent trials it has yielded encouraging data. It is a new anti-fibrotic agent that suppresses the production of inflammatory cytokines. Studies in the US and Japan suggest that this drug may have a stabilizing effect on disease progression. In the phase II study done in USA, Pirfenidone was given for up to 2 years in 54 patients and in those followed up till one year there was improvement or stabilization in of lung function. Similar beneficial results have been observed in the Japanese studies and drug has now been approved for use in Japan. Overall, collective data from randomized, double-blind, placebo-controlled pivotal studies provide evidence that pirfenidone provides a clinically meaningful benefit to patients by reducing decline in lung function.

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- The commonest adverse event is photosensitivity. Other adverse events were most often mild-to-moderate in severity, non-serious, readily monitored, reversible, and without significant clinical consequence.
- Conducting clinical trials in India in IPF can be challenging and difficult. Some of the reasons have been mentioned in your letter. IPF is uncommon and conducting trials needs a multicenter study with difficulties in definite diagnosis and follow up. Also a placebo control would be needed since what studies examine is prevention of worsening rather than improvement and use of a placebo may be difficult to justify.

Therefore it is my recommendation that Pirfenidone be made available in India on an early basis based upon the available published data and the unmet medical need of these patients.

Thanking you,

Yours faithfully,



19/6/10

Dr. Randeep Guleria
 Prof. of Medicine
 AIIMS, Ansari Nagar
 New Delhi

[Faint handwritten notes and stamps on the right side of the page]

DR. PRALHAD P. PRABHUDESAI

M.D. (Mum.) D.N.B.
Consultant Chest Physician

For Appointment : After 4.00 p.m
Contact : 6500 5856/9892038

OM CLINIC

14/101, 1st Floor, 'A' Wing,
Anand Vatika CHS, Above Citi Financi
S. V. Road, Goregaon (W), Mumbai-62
Monday to Friday : 7.00 to 9.30 p.m.
Fax : 022-2878 7131

ATTACHMENTS :

Lilavati Hospital : ☎ 2642 1111/2655 2222
Gurunanak Hospital : ☎ 2659 2853 to 58

May 25, 2010

Mr. A. K. Pradhan
Asst. Drugs Controller General (India)
FDA Bhavan,
Kotla Road
New Delhi

Dear Mr. Pradhan,

I have received the file along with a letter regarding Pirfenidone 200 mg tablets.

Idiopathic Pulmonary Fibrosis is a debilitating fatal disease of unknown etiology. Although considered rare, we are increasingly seeing more patients. Diagnosis can be difficult and complex and is generally made when the disease has progressed significantly. There is no specific treatment for IPF and although steroids and immunosuppressives have been used they have a limited benefit. IPF therefore represents an urgent, unmet medical need.

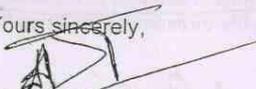
Pirfenidone is a synthetic, non-peptide molecule, a new molecular entity in a new pharmacological class. The drug regulates TGF-beta and TNF-alpha-mediated pathways in IPF. Studies have shown that drug seems to be effective in stabilizing the lung function and delaying progression of the disease. Importantly a beneficial effect has been shown in preventing exacerbations of the disease.

Conducting clinical trials of Pirfenidone in India in IPF is difficult for several reasons the main being a lack of uniformity in diagnosis and lack of validated endpoints for disease assessment. Since studies have been done in Japan and it has been approved for the indication since 2008, clinical trials may be waived. This would also help in making the drug available in India quickly.

The availability of Pirfenidone in India would be beneficial to patients with this disease and I would therefore strongly recommend that this drug be made available in India as early as possible.

Thanking you,

Yours sincerely,


Dr. P. Prabhudesai
Consultant Chest Physician
Lilavati Hospital & Research Centre
Mumbai


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IPA(S)
USPAG ABC (P)
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12

Department of Pulmonary Medicine

Postgraduate Institute of Medical Education & Research Chandigarh (India) - 160 012

Phone: (+91, 172) 2747585 Ext. 6821, 6823
Fax: (+91, 172) 2745959, 2744401

Email: dheeraj@indiachest.org
dheeraj88@hotmail.com

Dr. Dheeraj Gupta

MD, DM, FCCP, MAMS

Additional Professor

June 14, 2010

Mr. A. K. Pradhan
Asst. Drugs Controller General (India)
FDA Bhavan, Kotla Road,
New Delhi

Pulm - 1361
15/6/2010

Re: Desirability and essentiality of making Pirfenidone 200 mg tablets available in India for use in IPF

Sir,

Thank you for your letter dated 20.05.2010 and referring the matter regarding Pirfenidone and sending me the file.

Idiopathic pulmonary fibrosis is a relatively rare disease often referred to as an orphan disease. It usually occurs in people over the age of 50 years and can be challenging to diagnose. Once a diagnosis is made the prognosis is very poor with 50% mortality at about 3 years. Corticosteroids, azathioprine and more recently N-Acetyl Cysteine are used but there is no approved treatment for the disease.

Pirfenidone is the first approved drug for IPF and it is currently available in Japan. It has a novel mechanism of action and reduces the amount of transforming growth factor β , which is involved in the process of fibrosis.

The enclosed data shows that the drug has been found to be effective in stabilizing the progression of the disease by decreasing the rate of decline in vital capacity and reducing exacerbations over periods up to 1 year. Few adverse events associated with Pirfenidone like photosensitivity are easily manageable and in the studies a very few dropouts were seen due this.

IPF is a relatively rare disease and with strict criteria required for a clinical trial, it would be difficult to enroll sufficient number of patients. Also clear end points for IPF have not been validated and this sometimes makes it difficult to judge the efficacy of a drug in IPF.

Considering the fact that Pirfenidone is already approved in Japan and there is a fairly large amount of data available which shows that the drug is well accepted, I strongly recommend that Pirfenidone be made available in India at the earliest. It will be a significant addition to the armamentarium of existing medications for a rare, disabling and potentially life threatening condition like IPF

Thanking you, Kind regards

Yours sincerely,

(Dheeraj Gupta)

Encl: documents received in original.

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Residence : 79 Sector 24-A Chandigarh (160 023) Phone : 0172-2727219, 2727220



Dr. Vijai Kumar R
MD, DTCD, FCCP(USA), FAARC (USA)
Pulmonologist
Mobile : 98498 09444
Email: drvijaipulmo@yahoo.co.in

June 12, 2010

Mr. A. K. Pradhan
Asst. Drugs Controller General (India)
FDA Bhavan,
Kotla Road
New Delhi

Dear Mr. Pradhan,

Thank you for sending the papers regarding Pirfenidone 200 mg tablets for the use in Idiopathic Pulmonary Fibrosis for my opinion.

Idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic interstitial pneumonias (IIPs). Its etiology is unknown, but how this fibrotic process develops in the lung has been studied over the last 60 years. It is a relatively rare disease, afflicting those 50-70 years of age, slightly more common among men than women. However, for several reasons, is being diagnosed more often than a decade ago.

Treatment of IPF is highly controversial. Traditionally, corticosteroids, immunosuppressive or cytotoxic agents have been used, but these treatments are of unproven benefit and have potentially serious toxicities.

Pirfenidone is the first pharmacologic agent approved for the treatment of IPF. It is an antifibrotic agent with preclinical and clinical data to support its use in IPF. The safety profile of pirfenidone indicates that adverse events are primarily related to tolerability rather than morbidity. The adverse events are readily monitored, are typically reversible, and are nonlethal. Use of measures to improve tolerance and prompt identification and symptomatic management of intolerance as for many other similar drugs will enable the chronic use of pirfenidone in most patients with IPF.

Dr. Vijai Kumar R
4878 Abe (P)
277110

Ala
112
Tolkin
Law
217
TDA(S)

For Appointments : 27713333 (Extn) 148/ 149
Behind Hari Hara Kala Bhavan, S.P. Road, Secunderabad-500 003. A.P. Ph: 2771 3333 Fax: 040 - 2770 3999
e-mail : secunderabad@yashodahospitals.com website : www.yashodahospitals.com



The totality of the data from the studies of pirfenidone, in the setting of this irreversible fatal disease and urgent unmet medical need, establishes for the first time a therapeutic option with a favorable benefit-risk profile and supports the approval of pirfenidone for the treatment of patients with IPF to reduce decline in lung function. Hence clinical trials may be waived for this drug.

We look forward to having this drug, Pirfenidone, as early as possible in India.

Thanking you,

Yours sincerely,

Vijai
12/6/2010
Dr. Vijai Kumar
Director & Professor,
Division of Pulmonary Medicine & Critical Care,
Yashoda Super Specialty Hospital,
Secunderabad

Dr. Hemant R. Pathak

M.S., M.Ch., D.N.B.
Professor & Head
Department of Urology
T. N. Medical College &
B. Y. L. Nair Ch. Hospital
Mumbai - 400 008. India.

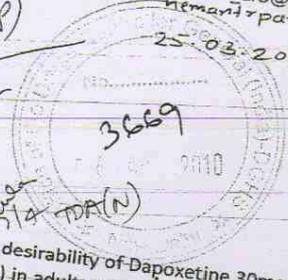
TEL :
Res. : 2494 0717, 2494 2809
Office : 2302 0092
2308 1490 Ext. 148
E-mail : hemant12@hotmail.com
hemant_uro@rediffmail.com
hemantpathak@gmail.com

15

ADCC(P)

ADCC

TO LINK



To,
Drugs controller General (India),
Directorate General of Health Services,
New Delhi.

Sir,
With regards to your letter requesting the opinion for desirability of Dapoxetine 30mg/60mg tablets for the treatment of premature ejaculation (PE) in adult male patients of 18-64 year age. I have pursued the literature provided and that is published till date.

Current therapeutic options available for the treatment of PE are limited, which include off-label use of SSRIs particularly like paroxetine and condoms containing local anaesthetics. Dapoxetine can offer several advantages over these for the treatment of PE.

1. Effectiveness of Dapoxetine is proven with on-demand intermittent dosing as can be inferred from the published clinical trials, review articles and regulatory approval documents provided in the literature.
2. Gastrointestinal side-effects are known to be the commonest adverse reactions with SSRIs; however they are dose related and are expected to be lower with on demand use of Dapoxetine as compared to currently recommended daily use of other SSRIs.
3. Risk of psychiatric and dermatological reactions does not appear to be substantial as can be inferred from the published literature till date.
4. Patient acceptability would be higher with oral medications like Dapoxetine as compared to medicated condoms.

In light of above, it may be stated that Dapoxetine can be a viable and safer therapeutic alternative in Indian patients for treatment of PE. It has been approved and is being marketed in several European countries presently.

I would like to thank you for asking my opinion as to examine the essentiality and desirability of the proposed medication.

Yours faithfully,
Hemant

Dr. HEMANT R. PATHAK,
Professor & Head,
Dept. of Urology,
T. N. Medical College &
B. Y. L. Nair Hospital,
Mumbai - 400 008.

2402/ADCC(P)110
T/4/10

②
2/11

17

Dr. Nilesh Shah

D. P. M., M. D. (Psychiatry), D. N. B. (Psychiatry)

Professor & Head, Department of Psychiatry,
OPD - 21, 1st Floor, College Building,
L.T.M. Medical College & General Hospital,
Sion, Mumbai - 400 022. Telefax : 2401 1984
Monday to Friday : 9.00 am to 4.00 pm
Saturday : 9.00 am to 1.00 pm

Consultant Psychiatrist : Pikale Hospital,
M.M. Chotani Marg, Cross Road-2, Mahim,
Mumbai - 400 016. Tel. : 2446 7138 / 2446 7295
Mon / Wed / Fri. : 5.00 pm to 7.00 pm

To,
Drugs controller General (India),
Directorate General of Health Services,
FDA Bhawan, Kotla Road,
New Delhi.



19.3.10
ADD (P)

Sub: Assessment of essentiality and desirability of Dapoxetine

Respected Sir,

With respect to your letter, dated 28th January, 2010 regarding the assessment of essentiality and desirability of Dapoxetine hydrochloride tablets in adult male patients suffering from premature ejaculation, I have pursued the literature provided with the letter.

As per the furnished documents, Dapoxetine hydrochloride 30 mg/60 mg tablets are proposed for the treatment of premature ejaculation in men of 18-64 years of age and have already been approved for marketing in European countries like Sweden, Finland, Germany, Italy, Spain, etc.

Premature ejaculation is a commonly encountered sexual disorder in clinical practice. In the event of failure of behavioural sexual therapy like stop-start or squeeze-pause techniques, no specific drug therapy is available till date. Anti-depressants like Paroxetine, Clomipramine, etc. and local anesthetics are used on an empirical basis for such patients.

Available literature shows that Dapoxetine is a novel SSRI which is effective for the treatment of premature ejaculation with on-demand dosing. As mentioned in the Public Assessment Report of Swedish authority, general safety profile of Dapoxetine is similar to other SSRIs and neuro-cognitive adverse events does not raise any major safety issues.

Concluding remarks can be made that, with proper patient selection as per the approved prescribing information in European countries, availability of Dapoxetine hydrochloride tablets should be advantageous and effective for the treatment of premature ejaculation, in comparison to current empirical treatment methods.

I am thankful for asking my views for essentiality and desirability of Dapoxetine.

Yours faithfully,

Nilesh Shah

19.3.10

DR. NILESH SHAH

Professor & Head,
Department of Psychiatry,
L.T.M. Medical College & General Hospital,
(Sion Hospital), Sion, Mumbai - 400 022.
Tel. : 2401 1984

2409/ADCU/10

7/4/10

20 1/4

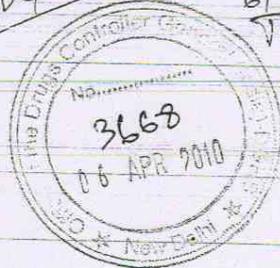
Department of Urology
Calcutta National Medical College
Kolkata-14

(16)

24.02.10

To
The Asstt. Drugs Controller
Directorate of General of Health Services
Office of Drugs Controller General(India)
(New Drug Division)
FDA Bhawan, Kotia Road, New Delhi.

ADC(P) →
Dh
6/4
7/19
TOBIN



Dear Sir

In ref. to your letter dated on 28th Jan 10, regarding Dapoxetine Hcl tablets marketing in India for treatment of premature ejaculation, I am here by submitting my reports.

Separate reports attached .

With thanks

Yours truly

Dilip Karmakar

Prof. Dr. Dilip Karmakar

2408/ADCE/10
7.19.10

Prof. Dilip Karmakar
M.S., M.Ch.(Uro)
Professor & Head of the Deptt. of Urology
Calcutta National Medical College
Kolkata - 700 014

GOVERNMENT MEDICAL COLLEGE, AURANGABAD**Dr. S.H. Talib**MD (Gen. Med.)
M.D. (Chest & TB)
FICA

Professor & Head,

Department of Medicine

Phone: 0240 2402424 Ext. 293

Res. : 0240 2390950, 2390750.

Fax : 0240 2402418

Email : shtalib_agd@sanchanet.in

Date : 17/8/05

To,
The Drug Controller General (India),
Directorate General of health services,
Nirman Bhawan,
New Delhi.Subject: Opinion on Nimesulide.
Reference: File no. 4-19/97-DC (Pt. PBL).

Sir,

This has reference to the above subject and would like to offer my comments as under. Nimesulide, NSAID, which possesses specific affinity to inhibit cyclooxygenase II. The drug has been under controversy for last one decade and has not been licensed in countries like UK, USA, Canada and Australia. The innovator of the drug, Boehringer, also had withdrawn the drug from Spain and Finland.

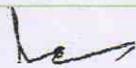
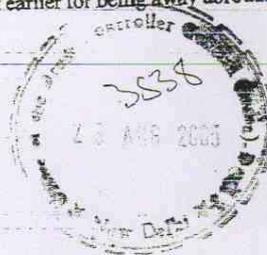
However, reviewing the drug literature and its toxicity, especially in adults, failed to show conclusively any greater ill side effects inclusive of hepatic toxicity, as a major enormous problem. The pharmaceutical properties, however impart potential clinical advantages to Nimesulide over other NSAIDs.

Toxicities of the Nimesulide are similar to that of Diclofenac and Ibuprofen and is not entirely free from nephrotoxicity. Nimesulide is able to affect all mediators of pain and inflammation resulting in desired long lasting analgesic and antipyretic effects. Hence its use in conditions associated with pain such as arthritis, ENT conditions, musculo-skeletal conditions, dental conditions and trauma seems promising. Drug is also suited in persons who are hypersensitive to aspirin like drugs.

To the best of my opinion Nimesulide injection may be advocated for short-term treatment of above cited inflammatory conditions.

I regret for not sending the report earlier for being away abroad.
Thanks,

Yours sincerely,


Dr. SH Talib.


D(P)



21

17th June 2005

To,

Mr. A.B. Ramteke
Joint Drugs Controller (India)
For Drugs Controller General (India)

Ref: File No. 4-19/97-DC(Pt.PBL)

Dear Mr. Ramteke,

This is in your reference your letter on 9th May 2005 regarding expert opinion on Nimesulide Injection.

I have gone through the published literature provided on Nimesulide. This literature supports its use for Orthopaedic and Non - Orthopaedic condition like ENT, Obstetrics & Gynaecology and Dental.

Yours sincerely,

Dr. RAJU VAISHYA (MS Orth, MCh Orth)
Sr. Consultant Orthopaedic Surgeon



Handwritten notes: (P), 27/8/05, 577/07

Handwritten notes: TCD 65R, 24/8/05



000
396

Sarita Vihar, Delhi-Mathura Road, New Delhi - 110 076, (INDIA)
Tel. : 26925801, 26925858 Emergency No. : 1066 Fax: 91-11-26823629



संस्थान में हिंदी मंत्रों का स्वागत है

①

भेषजबुध विज्ञान विभाग
स्नातकोत्तर चिकित्सा शिक्षा एवं अनुसंधान संस्थान, चण्डीगढ़ - १६००१२ (भारत)

DEPARTMENT OF PHARMACOLOGY
POSTGRADUATE INSTITUTE OF MEDICAL EDUCATION AND RESEARCH, CHANDIGARH - 160 012 (INDIA)
दूरभाष/Ph.(O):0172-2743451, 2756761, 2755241, (R): 2727354, फैक्स/Fax: 0172-2743451, 2744401, टेलिक्स/Telex:0396-735 PCIIN
ई-मेल/E-mail:ppandhi17@hotmail.com, Gram: POSTGRADMED

डॉ० (श्रीमती) प्रोमिला पांधी
प्राध्यापक एवं अध्यक्ष



Dr. (Mrs.) Promila Pandhi
M.D., D.M. (Clin, Pharm), MNAMS, FCP
Professor & Head

संख्या/No./Pharma- 07/259
दिनांक/Dated..... 1.3.67

To,
Themis Medicare Pvt. Ltd.,
11/12, Udyog Nagar,
S.V. Road,
Goregaon (W),
Mumbai.

Sub: Expert opinion for fixed dose combinations of drotaverine (80 mg) plus aceclofenac (100 mg) tablets.

I have studied the data provided by Themis Medicare Limited as regards the Fixed Dose Combination of drotaverine (80 mg) plus aceclofenac (100 mg) tablets for the use in conditions like Control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colic, cholecystopathy associated with spastic symptoms, cholelithiasis, cholecystitis, nephrolithiasis, peripheral arteries spasm, myometrium hyperactivity, smooth muscle spasms due to instrumental diagnostic procedures and neck of uterus spasm during delivery.

Drotaverine, a phosphodiesterase IV inhibitor, has an antispasmodic action without the antimuscarinic side-effects. It is currently used successfully in many countries for treating renal colic.

Aceclofenac, a phenylacetic acid derivative (2-((2,6-dichlorophenyl)amino) Phenylacetooxyacetic acid) related to diclofenac. It is a novel NSAID indicated for the symptomatic treatment of pain and inflammation.

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDs have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

The information provided with experimental & clinical references to Pharmacological actions and rationale seems to suggest that the combination would have added benefits to the patient. So in my opinion the combination of Drotaverine and aceclofenac would provide an effective pain relieving therapy.

Dr. Kalpana Ernest, M.D.
Professor & Head

Department of Pharmacology
&
Clinical Pharmacology,
Christian Medical College,
Bagayam, Vellore 632002, Tamilnadu, India.
E mail: drKapa@yahoo.co.in

+91-416 Res: 2264140
2284310
Off: 2284237

Date:.....

To,
M/s Themis Medicare Limited
11/12, Udyog Nagar Indl. Estate,
S. V. Road, Goregaon (West),
MUMBAI - 400 104

Date : 10.05.07

**SUB : Expert Opinion for Fixed Dose Combination of Drotaverine 80 mg with
Aceclofenac 100 mg Tablets**

I have examined the data provided by Themis Medicare Limited in respect of the Fixed Dose Combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets recommended in conditions like control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colic, cholecystopathy associated with spastic symptoms, cholelithiasis, cholecystitis, nephrolithiasis, peripheral arteries spasm, myometrium hyperactivity, smooth muscle spasms due to instrumental diagnostic procedures and neck of uterus spasm during delivery.

Drotaverine being a phosphodiesterase IV inhibitor, has a antispasmodic action without any antimuscarinic side-effects. It is currently successful in many countries for treating renal colic.

Aceclofenac, is a phenylacetic acid derivative (2 - ((2, 6 - dichlorophenyl) amino) Phenylacetooxyacetic acid) related to Diclofenac. Aceclofenac is a novel NSAID indicated for symptomatic treatment of pain and inflammation.

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDs have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

Based on the information provided to me which includes experimental and clinical references to pharmacological actions and rationale seem to suggest that the combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets would provide effective pain relieving therapy and also control and prevent pain and dysfunction caused by smooth muscle spasm.

To establish further safety and efficacy, clinical trials may be conducted.

Department of Pharmacology &
Clinical Pharmacology,
Christian Medical College,
VELLORE-632 002
S, INDIA.

Department of General Surgery

LOKMANYA TILAK MUNICIPAL MEDICAL COLLEGE AND GENERAL HOSPITAL
SION, MUMBAI - 400 022. (INDIA)

Tel. : (91-22) 4076381...90 (10 lines) • Ext. : Gen. Surgery 248 • Fax : (91-22) 4076100 E-mail : ltmsurg@bom2.vsnl.net

Ref : _____

Date : 9/3/2007

To,
Themis Medicare Ltd,
11/12 Udyog Nagar
S.V Road,
Goregaon (W)
Mumbai 400104

Sub:Expert Opinion for fixed dose combination of drotaverine(80 mg) plus aceclofenac(100 mg) tablets

I have studied the data provided by Themis Medicare Limited as regards the Fixed Dose Combination of drotaverine(80 mg) plus aceclofenac(100 mg) tablets for the use in conditions like Control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colics, cholecystopathy associated with spastic symptoms, cholelithiasis, cholecystitis, nephrolithiasis, peripheral arteries spasm, myometrium hyperactivity, smooth muscle spasms due to instrumental diagnostic procedures and neck of uterus spasm during delivery.

Drotaverine, a phosphodiesterase IV inhibitor, has an antispasmodic action without the antimuscarinic side-effects. It is currently used successfully in many countries for treating renal colic.

Aceclofenac, a phenylacetic acid derivative (2-((2,6-dichlorophenyl)amino)Phenylacetooxyacetic acid) related to diclofenac. It is a novel NSAID indicated for the symptomatic treatment of pain and inflammation

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDS have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

The information provided with experimental & clinical references to Pharmacological action and rationale seems to have added benefits to the patient. So in my opinion the combination of Drotaverine and aceclofenac would provide highly effective pain relieving therapy and also control and prevent pain and dysfunction caused by smooth muscle spasm.

To establish safety and efficacy further clinical trials are recommended


DR. SATISH B. DHARAP
M.S., D.N.B
Professor of Surgery:
L.T.M.M. College & L.T.M.G Hospital
Sion, BOMBAY-400 022



DEPARTMENT OF SURGERY

NILRATAN SIRCAR MEDICAL COLLEGE HOSPITAL

138, Acharya Jagadish Chandra Bose Road

Kolkata-700 014

Ref. No. To

Date : 22.3.07

Themis Medicare Pvt. Ltd.,
11/12, Udyog Nagar,
S.V. Road,
Goregaon (W),
Mumbai.

Sub: Expert opinion for fixed dose combinations of Drotaverine (80 mg) plus Aceclofenac (100 mg) Tablets.

I have studied the data provided by Themis Medicare Limited as regards the Fixed Dose Combination of Drotaverine (80 mg) plus Aceclofenac (100 mg) Tablets for the use in conditions like control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colics, cholecystopathy associated with spastic symptoms, cholelithiasis, cholecystitis, nephrolithiasis.

Drotaverine, a phosphodiesterase IV inhibitor, has an antispasmodic action without the anti-muscarinic side-effects. So it is more patient friendly drug. It is currently used successfully for treating renal colic.

Aceclofenac, a phenylacetic acid derivative (2-((2,6-dichlorophenyl) amino Phenylacetooxyacetic acid) related to Diclofenac. It is a novel NSAID indicated for the symptomatic treatment of pain and inflammation without the G.I. side effects of Diclofenac. This is more important when an oral preparation (Tablet) is used.

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDs have been successfully used to relieve pain. (Anti-muscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi).

As per rule when two drugs have same effect but have different mechanism of action they act synergistically. As is here mechanism of action of Drotaverine and Aceclofenac are completely different. So in my opinion combination of these two drugs in tablet form is rational and will be very useful for mild to moderate spasmodic pain of biliary and urinary system.

This is supported by information provided with experimental & clinical references to Pharmacological action.

Regards,

Bansari Goswami
Dr. Bansari Goswami
Professor & Head
Dept. of Surgery
NDS Medical College

Dr. D. ARVIND KUMAR M.D.

Prof. of Medicine
Gandhi Medical College / Hospital
Secunderabad.

Nagarjuna Polyclinic

Sebastian Road,
Secunderabad - 500 003.
Ph. : 7700733, 7701573
7715633, 7715634
Mobitel : 6271817

To,
M/s Themis Medicare Limited
11/12, Udyog Nagar Indl. Estate,
S. V. Road, Goregaon (West),
MUMBAI - 400 104

Date

SUB : Expert Opinion for Fixed Dose Combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets

I have studied the material provided to me by Themis Medicare Limited as regards the Fixed Dose Combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets recommended in conditions like control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colic, cholecystopathy associated with spastic symptoms, choledolithiasis, cholecystitis, nephrolithiasis, peripheral arteries spasm, myometrium hyperactivity, smooth muscle spasms due to instrumental diagnostic procedures and neck of uterus spasm during delivery.

Drotaverine is an effective antispasmodic, phosphodiesterase type IV inhibitor, which relieves smooth muscle spasm in all organs without any antimuscarinic side-effects and the same is currently used successfully in many countries for treating renal colic.

Aceclofenac is a non-steroidal anti-inflammatory agent, a phenylacetic acid derivative (2 - ((2, 6 - dichlorophenyl) amino) Phenylacetooxyacetic acid) related to Diclofenac.

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDs have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

The information on experimental and clinical references to pharmacological actions and rationale studied by me suggest that the combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets would provide effective pain relieving therapy and also control and prevent pain and dysfunction caused by smooth muscle spasm.

D. D. Arvind Kumar
Professor of Medicine
Gandhi Medical College
Civil Surgeon
Gandhi Hospital, Sec'bad

POST GRADUATE DEPARTMENT OF SURGERY
S.C.B. MEDICAL COLLEGE, CUTTACK

(Prof) Dr. Pramod Kumar Mallick
M.S. (Gen. Sur.)
Professor & HOD, Surgery

Phone : 0671-2414485 } (O)
0671-2422032 }
0671-2414570 } (R)
0671-2413123 }
Mobile: 9437013123

Ref.....

To,
M/s Themis Medicare Limited
11/12, Udyog Nagar Indl. Estate,
S. V. Road, Goregaon (West),
MUMBAI - 400 104

Date.....

Date : 07-05-07

**SUB : Expert Opinion for Fixed Dose Combination of Drotaverine 80 mg with
Aceclofenac 100 mg Tablets**

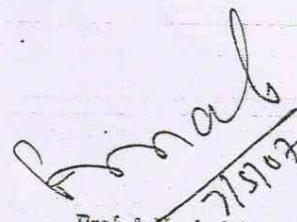
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Drotaverine is an effective antispasmodic, phosphodiesterase type IV inhibitor, which relieves smooth muscle spasm in all organs without any antimuscarinic side-effects and the same is currently used successfully in many countries for treating renal colic.

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Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDs have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

The information on experimental and clinical references to pharmacological actions and rationale studied by me suggest that the combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets would provide effective pain relieving therapy and also control and prevent pain and dysfunction caused by smooth muscle spasm.


Prof. & Head of the Department
of Surgery
S. C. B Medical College, Cuttack.

Dr. B. Prahlad

Regd. No. 7860 M.D. (Gen) D.C.H
PROFESSOR OF MEDICINE
& CIVIL SURGEON
Gandhi Medical College/Gandhi Hospital,
Secunderabad. A.P.

SWAMY CLINIC :

☎ : 27091085
12-10-713, Vyas Nagar,
Sitaphalmandi,
Secunderabad - 61.
TIMINGS :
5-00 p.m. to 9-00 p.m.

SUNDAY CLOSED

To,
M/s Themis Medicare Limited
11/12, Udyog Nagar Indl. Estate,
S. V. Road, Goregaon (West),
MUMBAI - 400 104

Date

SUB : Expert Opinion for Fixed Dose Combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets

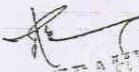
I have studied the material provided to me by Themis Medicare Limited as regards the Fixed Dose Combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets recommended in conditions like control and prevention of pain and dysfunction caused by smooth muscle spasm, biliary and renal colic, cholecystopathy associated with spastic symptoms, cholelithiasis, cholecystitis, nephrolithiasis, peripheral arteries spasm, myometrium hyperactivity, smooth muscle spasms due to instrumental diagnostic procedures and neck of uterus spasm during delivery.

Drotaverine is an effective antispasmodic, phosphodiesterase type - IV inhibitor, which relieves smooth muscle spasm in all organs without any antimuscarinic side-effects and the same is currently used successfully in many countries for treating renal colic.

Aceclofenac is a non-steroidal anti-inflammatory agent, a phenylacetic acid derivative (2 - {(2, 6 - dichlorophenyl) amino} Phenylacetooxyacetic acid) related to Diclofenac.

Prostaglandins have also been implicated in the etiology of biliary colic and NSAIDs have been successfully used to relieve pain. Antimuscarines have been tried for their action on biliary smooth muscle and sphincter of Oddi.

The information on experimental and clinical references to pharmacological actions and rationale studied by me suggest that the combination of Drotaverine 80 mg with Aceclofenac 100 mg Tablets would provide effective pain relieving therapy and also control and prevent pain and dysfunction caused by smooth muscle spasm.


DR. B. PRAHLAD
PROFESSOR OF MEDICINE
& CIVIL SURGEON
Gandhi Medical College
& Gandhi Hospital,
Secunderabad A.P.

DRUG INTERACTIONS:

Deanxit may enhance the response to alcohol, barbiturates and other CNS depressants. Simultaneous administration of MAO-inhibitors may cause hypertensive crises. Neuroleptics and thymoleptics reduce the antihypertensive effect of guanethidine and similar acting compounds and thymoleptics enhance the effects of adrenaline and noradrenaline.

INCOMPATIBILITIES:

Not known

PRESENTATION:

Ab blister pack strip of 10 tablets
10 strips in a carton.

Made in India by:
Lundbeck India Pvt. Ltd.
At:
B-249/250, 2nd Stage,
Peenya Industrial Estate, Bangalore 560 058.

Mfg. Lic. No.: KTK/25A/582/2005

Under Licence from:
H.Lundbeck A/S, Denmark.

Regd. Office:
Esteem Regency, II Floor,
6/A, Richmond Road,
Bangalore 560 026

© Trade Mark

LU/3/DX/A/0406 140x120

For the use of a registered Medical Practitioner or a Hospital or a Laboratory only.

Rx
FLUPENTIXOL AND MELITRACEN TABLETS
Deanxit

Mood - stabilizer

SCHEDULE H DRUG

Warning: To be sold by retail on the prescription of a Registered Medical Practitioner only.

COMPOSITION:

Each sugar-coated tablet contains:
Flupentixol Dihydrochloride, B.P.
equivalent to Flupentixol 0.5 mg
Melitracen Hydrochloride
equivalent to Melitracen 10.0 mg
Colours : Erythrosine and Indigocarmine

PHARMACOLOGICAL INFORMATION:

Pharmacological effects

Deanxit consists of two well known and well proved compounds: flupentixol-a neuroleptic with anxiolytic and antidepressant properties of its own when given in small doses, and melitracen-a bipolar thymoleptic with activating properties in low doses. The combination of the compounds render a preparation with antidepressant, anxiolytic and activating properties.

Pharmacokinetics

Maximal serum concentration is reached in about 4 hours after oral administration of flupentixol and in about 4 hours after oral administration of melitracen. The biological half-life of flupentixol is about 35 hours and that of melitracen is about 19 hours. The combination of flupentixol and melitracen does not seem to influence the pharmacokinetic properties of the individual compounds.

INDICATIONS:

Anxiety - Depression - Apathy.
Psychogenic depression, Depressive neuroses.
Masked depression. Psychosomatic affections accompanied by anxiety and apathy. Menopausal depressions. Dysphoria and depression in alcoholics and drug-addicts.

CONTRAINDICATIONS:

The immediate recovery phase after myocardial infarction. Defects in bundle-branch conduction. Untreated narrow angle glaucoma. Acute alcohol, barbiturate and opiate intoxications. Deanxit should not be given to patients who have received a MAO-inhibitor within two weeks. Not recommended for excitable or overactive patients since its activating effect may lead to exaggeration of these characteristics.

ADVERSE EFFECTS:

In the recommended doses side effects are rare. These could be transient restlessness and insomnia.

DOSAGE:

Adults: Usually 2 tablets daily: morning and noon. In severe cases the morning dose may be increased to 2 tablets.
Elderly patients: 1 tablet in the morning.
Maintenance dose: Usually 1 tablet in the morning. In cases of insomnia or severe restlessness additional treatment with a sedative in the acute phase is recommended.

OVERDOSAGE:

Symptoms: In cases of overdosage the symptoms of intoxications by melitracen, especially of anticholinergic nature, dominate. More rarely extrapyramidal symptoms due to flupentixol occur.

Treatment: Symptomatic and supportive. Gastric lavage should be carried out as soon as possible and activated charcoal may be administered. Measures aimed at supporting the respiratory and cardiovascular systems should be instituted. Epinephrine (adrenaline) must not be used for such patients. Convulsions may be treated with diazepam and extrapyramidal symptoms with biperiden.

PRECAUTIONS:

If previously the patient has been treated with tranquilizers with sedative effect these should be withdrawn gradually.

USE DURING PREGNANCY AND LACTATION:

Deanxit should preferably not be given during pregnancy and lactation.

add
N/A

No.4-97/89-DC

Nirman Bhawan, New Delhi
Dated the : 11th Feb'2000

19 FEB 2000

From :

The Drugs Controller General (India)
Dte. General of Health Services
Nirman Bhawan,
New Delhi-110011

To :

M/s Albert David Ltd.,
15 Chitranjan Avenue,
Calcutta-700072

Sub :- Placentrex Gel

Ref :- Your letter No. IR/ADL/DGHS dated 7th Feb'2000

Dear Sir,

As Placental extract is not a new drug , you are requested to contact the State Licensing Authority for obtaining necessary licence to manufacture the said product. This Dte. has however, no objection for Placentrex gel for treatment of Burns & Wounds, Non Healing - Inciscent Ulcers, Bed Sores, Oral Mucositis etc.

Yours faithfully,

(A.B. Ramteke)

For Drugs Controller General (India)

Copy to :-

Director, Drugs Control Administration, West Bengal, 141, A.J.C. Bose Road, Calcutta-700014 for necessary action.

(A.B. Ramteke)

For Drugs Controller General (India)

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated. Please read carefully before using a new pack.

Baralgan M™

Analgin

Baralgan M™ TABLET

Each tablet contains

Analgin I.P.500mg

DESCRIPTION

Metamizole sodium (INN), dipyrone (BAN, USAN), analgin
Pyrazolone derivative. Analgesic. Antipyretic.
Spasmolytic.

INDICATIONS

Severe or resistant pain and fever.

DOSAGE AND ADMINISTRATION

The dose depends on the severity of the pain or fever and the sensitivity of the individual's reaction to Baralgan M™. Essentially the lowest dose effective in controlling the pain and fever should be selected. In fever, a dose of 10 mg analgin per kilogram body weight is generally adequate in children. A clear effect can be expected 30 to 60 minutes after oral use.

For children and adolescents up to 14 years of age, the single dose is 8 to 16 mg analgin per kilogram body weight. Adults and young people aged 15 and over (> 53 kg) can take up to 1000 mg per single dose. In the event of inadequate efficacy the single dose may be given up to 4 times a day.

The recommended single doses and maximum daily doses are shown in the dosage tables below.
Dosage table for Baralgan M tablets 500 mg:

Age (body wt.)	Single dose	Maximum daily dose
10-14 years	1 tablet	up to 4 tablets
(31- 52 kg)	(equivalent to	(equivalent to

- Allergy to any of the excipients of Baralgan M™.
- Acute intermittent hepatic porphyria (risk of induction of porphyria attacks).
- Congenital glucose 6 phosphate dehydrogenase deficiency (risk of hemolysis).
- Infants under 3 months of age or 5 kg body weight.
- Pregnancy (see "Pregnancy")
- Lactation (see "Lactation")

WARNINGS

Agranulocytosis induced by analgin is an accident of immuno-allergic origin lasting for at least one week. These reactions are very rare, may be severe and life threatening, and could be fatal. They are not dose dependant and may occur at any time during treatment. All patients should be advised to stop medication and consult their physician immediately if any of the following signs or symptoms possibly related to neutropenia occur: fever, chills, sore throat, ulcerations in oral cavity. In the event of neutropenia (< 1,500 neutrophils/mm³) treatment should be immediately discontinued and complete blood count should be urgently controlled and monitored until they return to normal values.

Anaphylactic shock: These reactions occur principally in sensitive patients. Therefore, analgin should be prescribed with caution in asthmatic or atopic patients (See "Contraindications").

PRECAUTIONS

▪ Anaphylactic/anaphylactoid reactions

When choosing the route of administration, it must be taken into consideration that parenteral administration is associated with a higher risk of anaphylactic/anaphylactoid reactions.

In particular, the following patients are at special risk for possibly severe anaphylactoid reactions to analgin:

- Patients with bronchial asthma, particularly those with concomitant rhinosinusitis polyposa.
- Patients with chronic urticaria.
- Patients with alcohol intolerance, i.e. patients reacting to even minor quantities of certain alcoholic beverages with symptoms such as sneezing, lacrimation and pronounced redness of the face. Alcohol intolerance

IMPORTANT

Announcement on **DEANXIT**

An original research product of H Lundbeck, Denmark

Deanxit has been approved by Drug Controller General of India after mandatory clinical trials. The regulatory Phase III trial were conducted at Lady Hardinge Hospital, New Delhi and at Institute of Psychiatry and Human Behaviour, Goa. Further Deanxit has also been subjected to extensive post-marketing surveillance study on large Indian population in India for safety and tolerability.

Deanxit-a safe anxiolytic antidepressant, is approved and marketed in over 20 countries, including Switzerland, Austria, Spain, and Singapore among others.

Deanxit is approved by Danish Medicines Agency for manufacture in Denmark and for export.

Deanxit has over 40 years of international repute and has been prescribed to nearly 100 million patients world wide.

Deanxit has not been banned in any country or has been asked to be withdrawn by any Authority of any country.

Lundbeck complies with pharmacovigilance obligations globally and there has been no known serious adverse effect on Deanxit reported in India or elsewhere.

Lundbeck



Issued for the information of medical profession by

Lundbeck India Private Ltd

Regd Office: Esteem Regency, Fl 2

6 A, Richmond Road

Bangalore 560 025